

# Initiative for Vaccine Research

2004–2005  
Strategic Plan

**Immunization, Vaccines and Biologicals**



UNAIDS



World Health Organization



---

**The Department of Immunization, Vaccines and Biologicals  
thanks the donors whose unspecified financial support  
has made the production of this publication possible.**

### **Acknowledgements**

Grateful acknowledgement is made to the Rockefeller Foundation for funding the preparation of the IVR Strategic Plan 2004-2005. Thanks are extended to Irina Serdobova for her expert advice on core strategic and conceptual issues, and to all those involved in its development under the leadership of the Director of IVR, Marie-Paule Kieny. Editing was undertaken by Alison Rowe and finalized by Francis Carol.

This publication was produced by the  
Initiative for Vaccine Research of the  
Department of Immunization, Vaccines and Biologicals

*Ordering code: WHO/IVB/04.13  
Printed: November 2004*

**This publication is available on the Internet at:**  
[www.who.int/vaccines-documents/](http://www.who.int/vaccines-documents/)

**Copies may be requested from:**  
World Health Organization  
Department of Immunization, Vaccines and Biologicals  
CH-1211 Geneva 27, Switzerland  
• *Fax:* + 41 22 791 4227 • *Email:* [vaccines@who.int](mailto:vaccines@who.int) •

© World Health Organization 2004

All rights reserved. Publications of the World Health Organization can be obtained from Marketing and Dissemination, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel: +41 22 791 2476; fax: +41 22 791 4857; email: [bookorders@who.int](mailto:bookorders@who.int)). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to Publications, at the above address (fax: +41 22 791 4806; email: [permissions@who.int](mailto:permissions@who.int)).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

Printed by the WHO Document Publication Services, Geneva, Switzerland.

---

# Contents

<i>Abbreviations</i> .....	<i>v</i>
<i>Glossary</i> .....	<i>ix</i>
<i>Executive summary</i> .....	<i>xi</i>
<b>Part 1: Background</b> .....	<b>1</b>
1.1 Global burden of vaccine-preventable diseases .....	1
1.2 Global publicly funded research and development .....	3
1.3 Background to the formation of IVR.....	7
1.4 Unification towards a common goal .....	8
1.5 IVR's structure .....	8
1.6 IVR's mission .....	12
1.7 IVR's resource mobilization.....	12
<b>Part 2: Driving forces for vaccine research</b> .....	<b>13</b>
2.1 General driving forces for vaccine research .....	13
2.2 Key vaccine-oriented international initiatives .....	14
<b>Part 3: Priority setting</b> .....	<b>20</b>
3.1 Priority-setting.....	20
3.2 Support for vaccine R&D technology and practices .....	27
<b>Part 4: IVR strategic plan 2004-2005</b> .....	<b>31</b>
4.1 Objectives and milestones .....	31
4.2 IVR's workplan and budget .....	62
<b>Annex 1: IVR's role, by disease (in alphabetical order)</b> .....	<b>63</b>
<b>Annex 2: Human resources and professional backgrounds</b> .....	<b>72</b>

---

# Abbreviations

<b>AD</b>	auto-disable (syringes)
<b>AAVP</b>	African AIDS Vaccine Programme
<b>ADIP</b>	Accelerated Development and Introduction Plan
<b>AIDS</b>	Acquired Immunodeficiency Syndrome
<b>ANRS</b>	Agence Nationale de Recherches sur le Sida (France)
<b>ARIs</b>	Acute respiratory infections
<b>ATT</b>	Access to Technology, WHO
<b>BCG</b>	bacille Calmette-Guérin (vaccine)
<b>CDC</b>	Centers for Disease Control
<b>CDS</b>	Communicable Diseases Cluster, WHO
<b>CFs</b>	colonization factors
<b>CVD</b>	Center for Vaccine Development, Baltimore, Maryland, USA
<b>cVDPV</b>	circulating vaccine-derived polioviruses
<b>CVP</b>	Children's Vaccine Program at PATH
<b>DALYs</b>	disability-adjusted life years
<b>DF</b>	dengue fever
<b>DHF</b>	dengue haemorrhagic fever
<b>DOMI</b>	Diseases of the Most Impoverished
<b>DNA</b>	deoxyribonucleic acid
<b>DTP</b>	diphtheria-tetanus-pertussis vaccine
<b>EMEA</b>	European Agency for the Evaluation of Medicinal Products
<b>EMVI</b>	European Malaria Vaccine Initiative
<b>EPI</b>	Expanded Programme on Immunization
<b>ETEC</b>	enterotoxigenic <i>Escherichia coli</i>
<b>FML</b>	Fucose-mannose Ligand
<b>EU</b>	European Union
<b>GAVI</b>	Global Alliance for Vaccines and Immunization
<b>GCP</b>	good clinical practices
<b>GLP</b>	good laboratory practices
<b>GMP</b>	good manufacturing practices
<b>GPA</b>	Global Programme on Aids
<b>GPV</b>	Global Programme for Vaccines
<b>Hib</b>	<i>Haemophilus influenzae</i> type b

---

<b>HIV</b>	human immunodeficiency virus
<b>HPV</b>	human papillomavirus
<b>Hsp</b>	heat shock protein
<b>HTM</b>	HIV/AIDS, TB and Malaria Cluster, WHO
<b>HuCV</b>	human caliciviruses
<b>HVI</b>	Joint WHO-UNAIDS HIV Vaccine Initiative
<b>IAMI</b>	International AIDS Vaccine Initiative
<b>IBRD</b>	International Bank for Reconstruction and Development
<b>ICDDR,B</b>	Centre for Health and Population Research, Dhaka, Bangladesh
<b>IDA</b>	International Development Association
<b>ICH</b>	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
<b>IDRI</b>	Infectious Disease Research Institute
<b>IPD</b>	invasive pneumococcal disease
<b>IPV</b>	inactivated poliomyelitis vaccines
<b>IRB</b>	Institutional ethical review board
<b>iVDPV</b>	replicating polioviruses isolated from immunocompromized individuals
<b>IVI</b>	International Vaccine Institute
<b>IVR</b>	Initiative for Vaccine Research
<b>IVR/BAC</b>	Research on Bacterial Vaccine Research Team
<b>IVR/HVI</b>	Research team of the WHO/UNAIDS HIV Vaccine Initiative
<b>IVR/POP</b>	Parasitic and other pathogens vaccine research team
<b>JE</b>	Japanese encephalitis
<b>LPS</b>	lipopolysaccharide
<b>MALVAC</b>	Malaria Vaccine Advisory Committee
<b>MRC</b>	Medical Research Council
<b>MVI</b>	Malaria Vaccine Initiative
<b>MVP</b>	Meningitis Vaccine Project
<b>NCI</b>	National Cancer Institute (NIH, USA)
<b>NHMRC</b>	National Health and Medical Research Council
<b>NIH</b>	National Institutes for Health
<b>NRA</b>	National Regulatory Authority
<b>OPV</b>	oral poliomyelitis vaccine
<b>PATH</b>	Program for Appropriate Technologies in Health
<b>PAG</b>	Project Advisory Group for the Meningitis Vaccine Project
<b>PDG</b>	Product Development Group for the Measles Aerosol Project
<b>PDVI</b>	Paediatric Dengue Vaccine Initiative
<b>PKDL</b>	post-Kala Azar dermal leishmaniasis
<b>PVD</b>	Programme for Vaccine Development
<b>QSB</b>	Quality and Standardization of Biologicals, WHO
<b>RBM</b>	Roll Back Malaria/Partnership Secretariat
<b>R&amp;D</b>	Research and Development

---

<b>R&amp;PD</b>	research and product development
<b>RRV-TV</b>	Rhesus Rotavirus Reassortant Tetravalent Vaccine
<b>RSV</b>	respiratory syncytial virus
<b>RVP</b>	Rotavirus Vaccine Program
<b>SAGE</b>	IVB Strategic Advisory Group of Experts
<b>SARS</b>	severe acute respiratory syndrome
<b>SOP</b>	Standard Operating Practices
<b>STAC</b>	TDR Scientific and Technical Advisory Committee
<b>TB</b>	tuberculosis
<b>TBVAC</b>	Advisory Committee on new tuberculosis vaccines
<b>TDR</b>	UNICEF–UNDP–World Bank–WHO Special Programme for Research and Training in Tropical Disease
<b>UMC</b>	WHO Collaborating Centre for International Drug Safety Monitoring
<b>UNAIDS</b>	Joint United Nations Programme on HIV/AIDS
<b>UNICEF</b>	United Nations Children’s Program
<b>UNDP</b>	United Nations Development Program
<b>USAID</b>	United States Agency for International Development
<b>VAC</b>	HIV Vaccine Advisory Committee
<b>VAM</b>	Vaccine Assessment and Monitoring, WHO
<b>VAPP</b>	vaccine-associated paralytic poliomyelitis
<b>VLPs</b>	virus-like particles
<b>WRAIR</b>	Walter Reed Army Institute of Research
<b>YF</b>	yellow fever

---

# Glossary

<b>adjuvant</b>	<ol style="list-style-type: none"><li>1) A pharmacological agent added to a drug to increase or aid its effect.</li><li>2) An immunological agent that increases the immune response to a vaccine.</li></ol>
<b>antigenic drift</b>	minor antigenic variations caused by point mutations
<b>antigenic shift</b>	genetic exchange occurring between viruses infecting different animal species
<b>antimonial</b>	first line drug for cutaneous leishmaniasis and PKDL
<b>anthroponotic</b>	human-human transmission
<b>industrialized/ developing country</b>	<p>Adapted from the World Trade Organization. There are no WTO definitions of “industrialized/developed” and “developing” countries. Members announce for themselves whether they are “developed” or “developing” countries. However, other members can challenge the decision of a member to make use of provisions available to developing countries.</p> <p><b>What are the Developing Countries by Income:</b></p> <p><b>Low-Income Countries</b> (per capita GNP below US\$675 in 1992), <b>Low Middle-Income Countries</b> (\$676 – \$2,695), <b>Upper Middle-Income Countries</b> (\$2,696 – \$8,355), and <b>High-Income Countries</b> (above \$8,355).</p>
<b>DALY</b>	The DALY is a health gap measure, which combines information on the impact of premature death and of disability and other non-fatal health outcomes. One DALY can be thought of as one lost year of “healthy” life, and the burden of disease as a measurement of the gap between current health status and an ideal situation where every one lives into old age free of disease and disability.
<b>catch-up (campaign)</b>	A vaccination campaign designed to reach unreached members of the population
<b>cryoprotectant</b>	A substance used to protect cells or tissues from damage during freezing

---

**proteomics**

The identification, characterization and quantification of all proteins involved in a particular pathway, cell, tissue, organ or organism that can be studied in concert to provide accurate and comprehensive data about that system.

**zoonotic**

animal to human transmission

---

# Executive summary

Vaccines already protect millions of lives each year against infectious disease. In spite of this success, at least 15 million people each year are still dying from diseases that could be prevented by existing vaccines, or by vaccines that could be developed through targeted research and development.\* New vaccines could bring huge health gains in controlling the diseases that cause the most illness and death in the poorest regions of the world. Acute respiratory infections, HIV/AIDS, diarrhoea, tuberculosis, malaria, and measles are the leading killers, contributing substantially to the death toll of more than 1600 children every day and annually afflicting millions more adults and their families. Immunization would also be a key control measure for diseases like dengue, from which 50 million people globally are suffering.

The process of developing vaccines is lengthy, complex and expensive: it usually takes more than 10 years to arrive at a fully licensed product. The investment is enormous and as a result those who most need the vaccines are the least able to afford them. Commercial realities have tended to push vaccine research and development towards products for infectious diseases present in the industrialized world, leading to a dramatic shortage in investments in preventive tools for diseases of poor and “neglected populations”.

The Initiative for Vaccine Research (IVR) is WHO’s response: an international team of highly qualified project managers, scientists and technical experts whose task it is to facilitate the development of vaccines against major infectious killer or crippling diseases, and to ensure that they are made available to the people that need protection most.

In this context, IVR’s vision is to **develop and promote a global and sustainable research and development pipeline delivering the optimal vaccines for WHO vaccine research and development (R&D) priority diseases.**

This Strategic Plan describes IVR’s planned areas of work over the timeframe 2004-2005, and analyses the approach to developing vaccines against each priority disease. The Plan looks at every infectious disease of public health significance and applies a *filtering system* to create a shortlist for action. **If the disease has no effective vaccine, if alternative treatment tools available cannot keep the disease under control, and if there is not enough commercial interest to ensure global access to such a vaccine, it becomes an IVR priority.** The Initiative then has three possible roles to play in working with its many partners to see the long process through to

---

\* Statistics adapted from *The World Health Report, 2002 (4)*, World Health Organization, Geneva, 2002.

---

get the right vaccine developed. Firstly, as “*developer*” IVR directly supports some of the associated research and management tasks, and actively uses its linking and convening strengths to create partnerships and co-sponsor relationships to support others. In this context IVR is a developer for vaccines against leishmaniasis, malaria, measles, meningitis A, and immunoglobulins against rabies. Secondly, IVR is a “*facilitator*”, in instances where there are many other parties involved in one capacity or another, for example, in the work to accelerate the development of an improved vaccine against tuberculosis. In this role IVR is an independent, objective process consultant and strategic or technical adviser for ongoing global research and product development. IVR is a facilitator for work on vaccines against dengue, HIV/AIDS, *S. Pneumoniae*, tuberculosis, cervical cancer (HPV), influenza, Japanese encephalitis, rotavirus, *Shigella* and enterotoxigenic *Escherichia coli*-associated diarrhoea, as well as SARS. Thirdly, IVR is “*watchful waiting*”; an oversight role which speaks for itself: the diseases in this group may well move to either of the other two categories as the global R&D pipeline develops, and partnerships strengthen. Examples of these diseases are caliciviruses, cholera, typhoid fever, Buruli ulcer or schistosomiasis.

Where there are obstacles in the vaccine “pipeline”, IVR’s mandate is to **find creative solutions to funding shortfalls**, to **provide expert scientific knowledge** to facilitate breakthroughs, and to **partner with the international vaccine community** to accelerate access. In WHO, IVR is the key body responsible for drawing together the necessary expertise and efforts to address both worldwide priorities and to strengthen capacity for vaccine research and development. Although it is not a funding agency, the Initiative can provide seed funds or bridging financing grants for development projects, and small grants for basic research and developing platform technologies as recommended by the IVR steering committees. IVR has the versatility and flexibility to use different mechanisms depending on the particular issue and the convening power to call together all relevant parties, including the private sector, to reach consensus on R&D priorities, and to engage them in projects and initiatives, drawing on their knowledge and expertise in disease control, as well as in regulatory and policy matters. Once those challenges have been identified, IVR can quickly respond with the help of advisory bodies and governing structures that represent a wide global constituency.

Because the Initiative is free from commercial or national influences or lobbying, it is independent in its opinions and judgements. As an “impartial broker” it can coordinate processes among partners and communities, working as a powerful advocate for developing countries’ needs and providing management support for new initiatives, for example, the recently launched African AIDS Vaccine Programme.

IVR staff work in close association with a very wide range of WHO units such as the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), the Communicable Diseases (CDS) cluster, the HIV, Tuberculosis and Malaria (HTM) cluster and initiatives like the Stop TB and Roll Back Malaria Partnerships. It is also a counterpart within WHO for external partners and organizations like UNAIDS, the Global Alliance for Vaccines and Immunization (GAVI), the Program for Appropriate Technologies in Health (PATH), the International Vaccine Institute (IVI), as well as the many other public and private sector partners in vaccine R&D, whose contributions to the “pipeline” are vital.

Good communication is an essential part of making this vast global partnership work. The aim of this Strategic Plan is firstly to contribute to a clear understanding of

---

IVR's objectives and proposed activities so that coordinated workplans can be made, secondly, this Strategic Plan is intended to present a scenario that stimulates other potential partners to invest in R&D for vaccines against infectious diseases affecting the poor.

**IVR's mission :**

"To guide, provide vision, advocacy, coordination, guidance and support to enable the development of safe, effective, affordable and accessible vaccines against infectious diseases of public health importance, especially in developing countries."

---

# Part 1:

## Background

### 1.1 Global burden of vaccine-preventable diseases

The world's developing countries suffer greatly as a result of the premature deaths and disability caused by infectious diseases for which vaccines need to be improved or do not yet exist. Worldwide, infectious diseases are responsible for one-third of all deaths, killing at least 15 million people each year. Moreover, the health disparity between industrialized and developing countries is reflected in the average life spans in these two settings (77 vs 52 years, respectively), and deaths attributable to infectious diseases contribute largely to the observed lack of parity in life expectancy.<sup>1</sup> Of those deaths, over 2.7 million (63%)<sup>2</sup> are among children under five years of age. At least two million children from developing countries die each year from diseases that could have been prevented by vaccines that already exist. Beyond this high death toll, millions more children suffer disability and illness because they were not immunized. By helping to reduce the burden of disease, new, improved and more accessible vaccines contribute to the global efforts to reduce poverty.

Acute respiratory infections (ARIs) remain the most important cause of paediatric mortality, accounting for about 3 million deaths each year and ranking first among the causes of disability-adjusted life-years (DALYs) lost in developing countries (90 Millions, 6.1 % of total).<sup>3</sup>

The HIV pandemic now affects more than 42 million people, with more than 15 000 new infections every day. HIV/AIDS kills more people than any other single infectious disease, causing more than 3 million deaths every year. HIV/AIDS already ranks as the first cause of death in Africa, and the fourth in the world.

Diarrhoeal diseases kill more than 1.7 million children below five years of age, ranking third among all causes of disease burden worldwide. Five diseases (cholera, enterotoxigenic *Escherichia coli*-associated diarrhoea, typhoid fever, dysentery and rotavirus diarrhoea) are responsible for most of the deaths.

---

<sup>1</sup> Widdus R. Public-private partnerships; their main targets, their diversity, and their future directions, *Bulletin of the World Health Organization*, 2001, 713: 720–79.

<sup>2</sup> *Removing obstacles to healthy development*. World Health Organization, Geneva, 1999.

<sup>3</sup> *The World Health Report 2003: Shaping the future*, Annex Table 3: 160–5. World Health Organization, Geneva, 2003.

---

These three major killers (ARIs, HIV/AIDS and diarrhoea) are closely followed by tuberculosis (about 1.6 million deaths per year<sup>4</sup>), malaria (1.2 million<sup>5</sup>) and measles (0.6 million<sup>6</sup>). Viral hepatitis also has an important impact on human health. Indeed, there are 350 million chronic carriers of hepatitis B virus, and at least another 100 million people with hepatitis C virus.

There are, however, reasons to be optimistic.<sup>7</sup> Vaccines are effective at combating diseases, as shown by the success of the polio eradication campaign that has managed to reduce the global incidence of this disease by more than 99%. Highly successful new vaccines are available against *Haemophilus influenzae* type b (*Hib*) and *Neisseria meningitidis* serogroup C. Combination vaccines have been developed to target several infectious agents simultaneously. Never before have there been so many candidate vaccines in various stages of development. The biotechnology revolution along with increased knowledge about immune responses is allowing the rational development of recombinant vaccines that may challenge such “difficult” diseases as HIV/AIDS, malaria and tuberculosis. As a result, an additional 12.5 million deaths from infectious diseases could be prevented by using the new vaccines that are projected to become available in the coming years (Fig. 1.1). All of these advances contribute to international efforts to achieve the Millennium Development Goals and should lead to a safer and more equitable world.

---

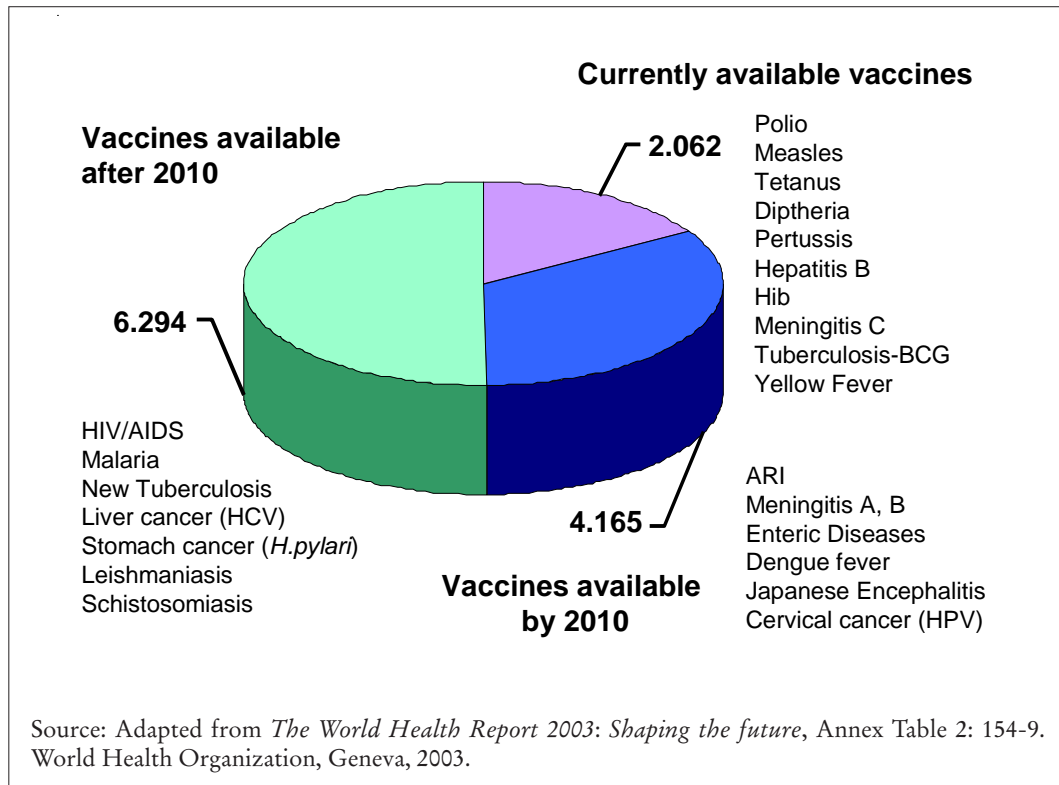
<sup>4</sup> *The World Health Report 2003: Shaping the future*, Annex Table 2: 154–9. Geneva, World Health Organization, 2003.

<sup>5</sup> Progress in reducing global measles deaths: 1999–2002. *Weekly Epidemiological Record*, 2004, 79: 20–1.

<sup>6</sup> *State of the World's Vaccines and Immunization*. Geneva, World Health Organization, 2002.

<sup>7</sup> *The World Health Report 2003: Shaping the future*, Annex Table 2: 154–9. Geneva, World Health Organization, 2003.

Fig. 1.1: The projected contribution of new vaccines to avoidable deaths (millions)



## 1.2 Global publicly funded research and development

The R&D process bridges the gap between scientific discoveries and tools available for health interventions. The main drive of the process is to design an effective production method for potential vaccine candidates, which are subsequently tested for safety and efficacy, first in experimental animals and ultimately in human volunteers, using the most appropriate scientific approaches and procedures. There is a clear responsibility throughout this process to comply with a structured framework of registration requirements and normative guidelines assuring ethics, safety, quality of research, manufacturing and development outcomes. The process for product R&D is consequently very complex. It often takes more than 10 years to arrive at a final licensed vaccine,<sup>8</sup> requiring not only excellence in R&D but also managerial and funding commitment throughout the endeavour.

Vaccine R&D is also an expensive and high-risk process. Viewed statistically, the product “pipeline” requires many early stage development projects to gain one successful product. Currently it is estimated that, to register a single vaccine there need to be 4.5 independent vaccine candidates under development, as the market entrance probability for preclinical vaccine candidates has been estimated at 0.22.<sup>8</sup>

<sup>8</sup> Struck MM. Vaccine R&D success rates and development times. *Nature Biotechnology*. 1996, 14: 591–593.

---

This results in an aggregate cost of US\$ 200–500 million per successfully developed new vaccine.<sup>9</sup> The uncertainty of research outcomes makes the pipeline a necessity, with a portfolio of vaccine candidates for each of the targeted diseases.

Successful vaccines available for immunization programmes today are the fruits of cumulative R&D carried out in past decades. Commercial vaccine R&D is financed through the delivery of profitable products whose returns offset development costs and provide funds for future technology and process development as well as increase the manufacturing company's share value. By definition, this commercial process will not address markets offering unacceptably low profit margins or those that are associated with high technological, marketing or political risks. As a result, less than 10% of global expenditure on health R&D is spent on developing vaccines for the major health problems of 90% of the world's population.<sup>10</sup>

From the outset, the economic situation for vaccine development within the private arena is bleaker than that for drugs. Vaccines are typically low-margin, non-chronic-use products that can often be associated with a high exposure to marketing risks. The worldwide vaccine market is estimated at approximately US\$ 6.5 billion, or about 2% of the global pharmaceutical market.<sup>11</sup> The lack of connection between society's need for vaccines and the willingness to pay for them has been widely discussed.<sup>12</sup> This disconnect is mainly due to a reluctance of individuals to invest in expensive vaccines for diseases they may never encounter, which as a consequence discourages private investment into vaccine R&D. Although the cost-effectiveness of investment in existing disease-control programmes that use vaccines is well established, the cost-benefit approach has not yet been effectively employed to attract public investment into vaccine R&D. In addition, the public funds allocated in the 1970s and 1980s to support academic scientific research in these areas were limited by the understandable lack of expertise among scientists to take product development beyond the stage of scientific publication and "proof of concept" in animals. As a result of these and other factors, combined with a protracted absence of private funding directed to particular pathologies, the concept arose of "neglected" diseases and "neglected" populations that had no access to medicines.

The ratios for poor-rich DALYs are highly variable according to the disease considered. For example, the world's poorest 20% experience more than 300 times the number of DALYs lost from malaria than the richest 20% of the population, whereas the ratio is around 11 for both sense organ disorders and perinatal conditions.

---

<sup>9</sup> Andre FE. How the research-based industry approaches vaccine development and establishes priorities. *Journal of developmental biology* (Basel). 2002;110:25–29.

<sup>10</sup> *The 10/90 Report on Health Research 2001–2002*, Davey S, ed., Global Forum for Health Research 2002.

<sup>11</sup> Greco M. The future of vaccines: an industrial perspective. *Vaccine*, 2001, 20 Suppl 1:S101–103.

<sup>12</sup> Rappuoli R, Miller HI, Falkow S. Medicine. The intangible value of vaccination. *Science*. 2002;297:937–939.

An analysis of current DALYs data (using the algorithm developed by Gwatkin and Guillot for the 1990 DALYs figures in Table 1.1) provides a very similar picture, with the exception of the burden of disease caused by HIV/AIDS. Indeed, *the World Health Report 2003* cites 86 072 000 DALYs lost globally for HIV/AIDS for 2002.<sup>13</sup> This is a marked increase from 10 400 000 (0.8% of 1.3 billion DALYs lost globally) for 1990. This huge rise would put HIV/AIDS in one of the very first ranks in Table 1.1. It is of note that for each of these diseases there is no effective vaccine currently available.

**Table 1.1: Number of DALYs lost by different population groups (1990)<sup>14</sup>**

Cause	Number of DALYs lost among global poorest 20% (in '000s)	Number of DALYs lost among global richest 20% (in 000's)	Poor-rich DALY ratio	Effective vaccine available
Malaria	18 387	61	301.43	No
Other TDR diseases: Trypanosomiasis, Chagas Disease, Schistosomiasis, Leishmaniasis, Lymphatic Filariasis, Onchocerciasis	5 547	31	178.94	No
Childhood cluster diseases: Pertussis, Poliomyelitis, Diphtheria, Measles, Tetanus	35 559	550	70.18	Yes
Diarrhoeal diseases	52 230	1 274	41.00	For typhoid/cholera
Tuberculosis	17 810	595	29.93	BCG
Maternal conditions	18 735	896	20.91	
Respiratory infections	55 911	3 165	17.67	For Hib and <i>S. pneumoniae</i>
Nutritional deficiencies	21 519	1 730	12.44	
Sense organ disorders	3 536	327	10.81	
Perinatal conditions	41 911	3 892	10.77	
HIV/AIDS	4 811	1 303	3.69	No

Note: Infectious diseases are shown in blue, non-infectious disorders in black.

<sup>13</sup> *The World Health Report 2003: Shaping the future*, Annex Table 3: 160-5. World Health Organization, Geneva, 2003.

<sup>14</sup> Adapted from Gwatkin DR, Guillot M. *The Burden of tropical diseases among the poorest and richest 20% of the global population*. TDR/ER/RD/96.1, World Health Organization, Geneva, 1998.

---

The traditional paradigm for introduction and use of new vaccines in the developing world has encountered many difficulties that have significantly delayed the introduction of vaccines to those who need them most. Firstly, vaccines are rarely developed against diseases for which the burden is prominent only or mostly in developing country populations with little risk for individuals in industrialized countries. High “opportunity” costs are a powerful deterrent to investment – in other words there is little incentive to invest in expensive development when other projects are perceived to offer a higher return on investment. Vaccines that are developed for a market in industrialized countries are almost always unaffordable for developing-country health systems. It is usually many years before the price of such vaccines drops to the extent that external aid donors and developing-country governments can buy them. Therefore, sustained public investment is required in vaccine R&D for specific target diseases which affect mainly “neglected” populations whose market characteristics fail to attract private capital. Without this, the rapid technological progress arising from targeted, commercially attractive vaccine development will not be effectively harnessed and integrated into programmes addressing underserved pathologies and populations. As a result, the most vulnerable will become even more disadvantaged.

It is vital to develop new vaccines continuously, or to improve existing vaccines. Through this process, the next generation of vaccines can replace the existing ones, thereby offering better safety, efficacy and delivery methods with lower costs of production and distribution to ensure effective coverage and accessibility. Research can also focus on the tailoring of vaccines to meet the challenges of new populations and emerging and unmet medical needs. For example, there is an urgent requirement for a new generation of influenza vaccines that can provide a more appropriate response to the ever-present threat of a new pandemic.

The development of combination vaccines is proceeding apace; new formulations are boosting an ever-growing array of antigens. All vaccine manufacturers are currently working towards developing different variations of multivalent vaccines by combining antigens such as inactivated poliovirus, conjugated *Haemophilus influenzae* type b polysaccharide and hepatitis B surface antigen to the diphtheria-tetanus-pertussis (DTP) vaccine either in its whole-cell or acellular pertussis formulation.

Today, most vaccines are administered as part of routine childhood immunization programmes. Over 100 million children are immunized every year throughout the world. It is estimated that 1.2 billion vaccine injections are performed every year and the number of antigens routinely administered is increasing rapidly. Moreover, the target age group for immunization is expanding to include older children, adolescents and young adults. Indeed, future vaccines will have an increasing role beyond infancy, targeting other specific ages or occupational groups: for example, the use of vaccines against sexually transmitted diseases in adolescence or a combined formulation providing prevention of respiratory infections for elderly people. To cope with this expansion, it is becoming increasingly evident that changes are needed to transform today’s immunization delivery system, making it broader, more equitable, efficient and safe. Indeed, most vaccines are administered parenterally, and it is anticipated that the majority of new vaccines that will be available by the

---

year 2005 will also be injectable. The number of immunization injections will thus increase from 1.2 to some 3.5 billion a year. Immunization via the oral or nasal route offers obvious advantages, including simplicity of administration and the possibility of also stimulating mucosal immune responses. Diverse antigen delivery systems are now being developed for the administration of vaccine antigens to mucosal surfaces.

To meet these challenges, a new paradigm needs to be built with WHO partners, including the pharmaceutical industries, emerging developing-country manufacturers, long-term R&D leaders such as the National Institutes of Health in the United States of America or the European Union, as well as the new players in global health like the Bill and Melinda Gates Foundation, among others. Most importantly, countries in the developing world will be playing an ever-increasing role in deciding which products they need and how they would like them to be administered, and WHO will play a critical role in making this happen.

WHO has traditionally provided leadership and vision to direct vaccine R&D to the diseases affecting the most needy. The inception of the Global Alliance for Vaccines and Immunization (GAVI), and the availability of its new, existing, or redirected resources, have together already changed the landscape of vaccine development. The Vaccine Fund has brought credibility to the concept that new vaccines can be introduced into the vaccination programmes of developing countries when provided at a reasonable price. WHO will make a determined response to these new opportunities and challenges to tackle the diseases of the poor.

### **1.3 Background to the formation of IVR**

Work to coordinate vaccine development has been ongoing in WHO and elsewhere for many years. In 1984 WHO established the Programme for Vaccine Development (PVD) to help develop new and improved vaccines for the future, working in collaboration with the Expanded Programme on Immunization (EPI). The Global Programme for Vaccines (GPV) was then created to deal with the vaccine continuum, with PVD providing the research and development component. In 1998 the department of Vaccines and Biologicals (now Immunization, Vaccines and Biologicals) was established in a further refinement of the organization of the vaccine programme and is currently part of the Family and Community Health cluster.

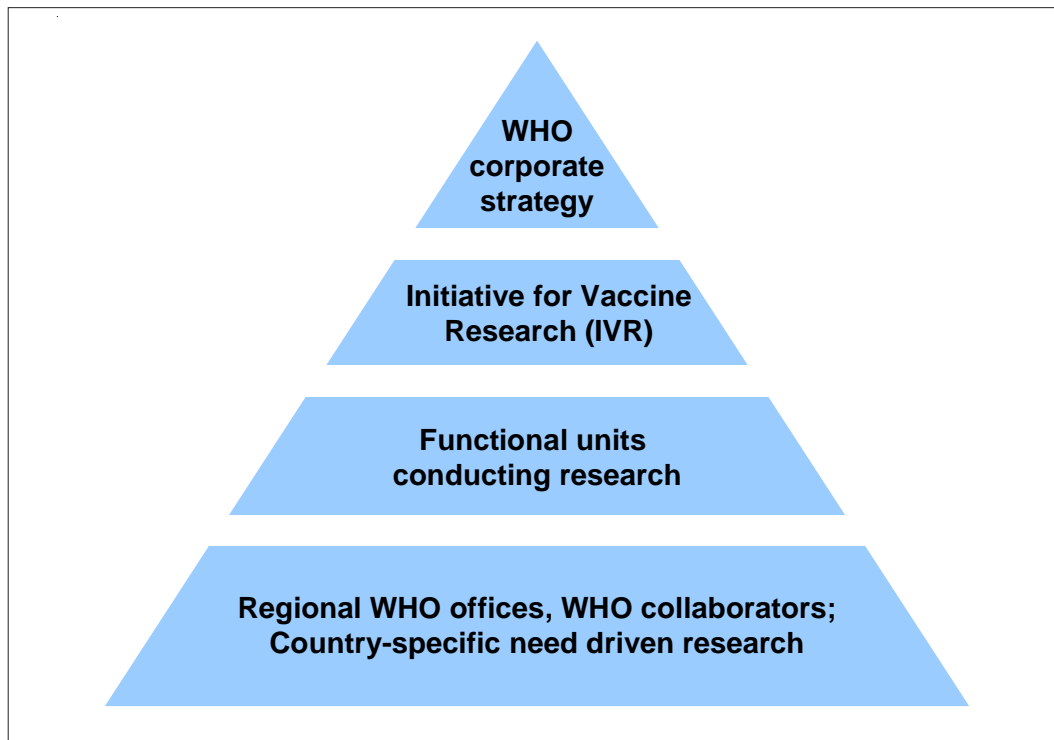
HIV vaccine activities in WHO were initiated in 1989, as part of the Biomedical Research Unit of the former WHO Global Programme on AIDS (GPA). In 1990 WHO/GPA established a dedicated “Vaccine Development Unit”, implementing a Strategic Plan aimed at promoting the development and evaluation of HIV vaccines appropriate for developing countries. With the establishment of UNAIDS in 1996, HIV vaccine activities were moved to the UNAIDS Vaccine Team. A joint WHO–UNAIDS HIV Vaccine Initiative (HVI) was further established, hosted in the Initiative for Vaccine Research.

---

## 1.4 Unification towards a common goal

IVR unites individual vaccine research functional units within the common vaccine research agenda as part of WHO's comprehensive health strategy (Fig. 1.2). The functional units rely on wide networks and partnerships of global and national research entities. The WHO research agenda targets the most needed areas, drawing on IVR's consultations with global public health research initiatives, donors and international research institutions. IVR also promotes independent research projects aligned with its strategic research priorities.

Fig. 1.2: Organization of vaccine research in WHO



## 1.5 IVR's structure

To reinforce linkages between vaccine R&D and the other components of immunization, IVR is located in the structure of the Department of Immunization, Vaccines and Biologicals (IVB) within the WHO Family and Community Health Cluster (FCH), and is led by a Director (appointed in December, 2001, see Annex 2 for details). The Director IVR is also the Secretary for the IVR Advisory Group (IVAC). IVR's workload is shared between three specialist team.

### 1.5.1 The IVR teams

Each of IVR's three teams is headed by a Coordinator. The areas of work described below are only indicative; they can be readjusted to best serve IVR's objectives and strategy to reflect current knowledge, skills, interest and resources.

- The IVR/BAC team works on vaccines against meningitis, diarrhoea, tuberculosis (TB), cervical cancer and other diseases as indicated by programme priorities. In addition, this team is responsible for the coordination of new vaccine delivery technology development.

- 
- The research team of the WHO/UNAIDS HIV Vaccine Initiative (IVR/HVI) is responsible for all aspects of research and development of new vaccines. In addition, the research and development on vaccines against Human Herpes Simplex virus type 2 (HSV2) is being incorporated in view of their potential role in the prevention of HIV transmission.
  - The IVR/POP team works on vaccines against vector-borne parasitic or viral infections like malaria, leishmania, dengue and Japanese encephalitis, and against acute respiratory infections as indicated by programme priorities. It is the focal point for interaction with the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Is also responsible for the coordination of efforts to strengthen vaccine and immunization research capacity-building and for research ethics within IVR.

### *1.5.2 Technical management*

The strategy, objectives and workplan of IVR are established following the recommendations of independent groups of international experts. The same groups have a mandate to review achievements against agreed milestones and to propose new avenues of research. Therefore, the management and guidance of the IVR takes place at three levels:

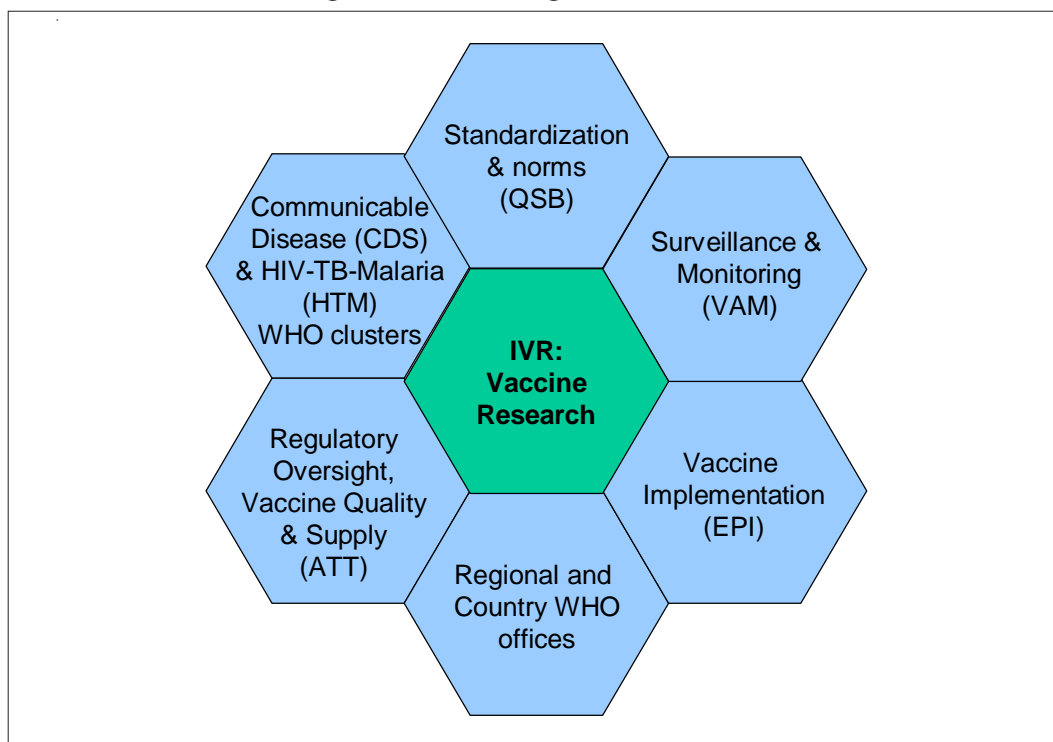
1. Internal review: IVR professional staff attend monthly meetings and periodically analyse two or three technical projects in depth.
2. Expert external review: **Steering or Advisory Committees** provide technical guidance on specific issues, whether on one particular disease, or a group of etiologically or symptomatologically linked diseases. These committees also review research proposals submitted to IVR for funding and usually meet annually.
  - List of IVR Steering/Advisory Committees:
  - Steering Committee on dengue and other flaviviruses vaccines
  - Steering Committee on research related to measles vaccines and vaccination
  - Steering Committee on new vaccine delivery systems
  - Steering Committee on diarrhoeal disease vaccines
  - Steering Committee of the African AIDS Vaccine Programme (AAVP)
  - Advisory Committee on new tuberculosis vaccines (TBVAC)
  - Advisory Committee for malaria vaccines (MALVAC)
  - HIV Vaccine Advisory Committee (VAC)
  - Product Development Group for the Measles Aerosol Project (PDG)
  - Project Advisory Group for the Meningitis Vaccine Project (PAG)
3. Overall technical and operational review: The **IVR Advisory Committee** was established to give overall technical and strategic guidance. The Committee comprises 10–12 experts (see Annex 2) who represent the broad range of biomedical sciences, product development and other disciplines required for IVR's activities.

IVR's workplan also takes into consideration the recommendations received from two other targeted advisory groups: the TDR Scientific and Technical Advisory Committee (STAC) and the IVB Strategic Advisory Group of Experts (SAGE).

### 1.5.3 *Liaison and networking*

Within WHO, IVR interacts closely with all other teams in the Department of Immunization, Vaccines and Biologicals and globally with other relevant WHO units (Fig. 1.3).

Fig. 1.3: IVR linkages within WHO



Note: QSB: Quality and Standardization of Biologicals; VAM: Vaccine Assessment and Monitoring; EPI: Expanded Programme on Immunization; ATT: Access to Technologies

WHO provides guidelines for the production and quality control of new vaccines through its Expert Committee on Biological Standardization. Therefore, interaction between IVR and the team working on Quality and Standardization of Biologicals (QSB), which is overseeing the process for the establishment of norms and standards, is crucial from the earliest stages of vaccine development. These guidelines are used as a basis for the product specifications used by the United Nations Children's Fund (UNICEF) and other United Nations vaccine procurement agencies, and thus are essential to WHO's prequalification system.

The ability of countries to make regulatory decisions on these new products must be addressed through a systematic effort to strengthen NRAs. In addition, novel ways need to be devised to provide specialized scientific support to NRAs of developing countries in the clinical evaluation of candidate vaccines. For this important aspect of work, IVR depends on the Access to Technologies team (ATT).

---

Demonstration projects in one or more countries may need to be conducted for some vaccines prior to their widespread introduction to evaluate the impact of vaccination, to assess the logistical feasibility of the vaccination programme and to build confidence with regard to the absence of adverse effects. Within WHO, the IVB team working on vaccine implementation (EPI) is responsible overall for this activity, in partnership with IVR. Appropriate epidemiological surveillance is deployed several years before vaccine introduction. Surveillance work is carried out by the Vaccine Assessment and Monitoring (VAM) team, and the WHO cluster on Communicable Diseases (CDS).

WHO has a considerable interest in the safety of vaccines, from the time of their early preclinical and clinical development to their safe use in practice after regulatory approval and post-marketing distribution. IVR has close links with the various WHO drug (and specifically vaccine) safety initiatives. In early development of new vaccines, when vaccine safety issues arise, WHO is able to call together independent experts who evaluate and predict vaccine safety issues. The advantages of this lie in both directions: bringing to a rapid halt any development that would predictably be later thwarted by safety issues and, conversely, avoiding cessation of a vaccine development programme because of an inappropriate and misguided concern for its safety.

In the pre-certification and drug registration process, and in pharmacovigilance after market authorization, WHO has a standing committee for reviewing vaccine safety issues with public health implications.<sup>15</sup> The WHO Collaborating Centre for International Drug Safety Monitoring (UMC), based in Uppsala, Sweden, coordinates the activities of more than 70 national pharmacovigilance centres worldwide that serve as contributing centres to the UMC. UMC has a database of more than 3 million adverse drug events reports, including vaccine safety reports, to which WHO, the contributing centres and other health authorities have ready access.

As part of its Global Training Network, WHO has trained more than 150 senior health professionals in national immunisation programmes and national drug regulatory authorities in vaccine safety detection and reporting.

Specific HIV vaccine activities are implemented together with UNAIDS and in collaboration with the HIV/AIDS programme of WHO. As research and development of vaccines against malaria and tuberculosis need to be integrated into the broader global perspective, IVR maintains close contact with the WHO cluster on HIV, Tuberculosis and Malaria, TDR, and the global initiatives to Roll Back Malaria and Stop TB.

IVR has a particular responsibility to involve developing countries in the flow and exchange of information. In this regard, links with regional and country offices are indispensable. Finally, IVR provides a single, easily identifiable WHO counterpart for partner agencies and organizations such as the Program for Appropriate Technology in Health (PATH), the International Vaccine Institute (IVI) in Seoul, Republic of Korea, as well as for many other public and private sector partners in vaccine R&D, in particular GAVI .

---

<sup>15</sup> Folb P et al., Vaccine safety and the public health – The World Health Organization Global Advisory Committee on Vaccine Safety, *American Journal of Public Health*, 2004, in press.

---

## 1.6 IVR's mission

The Director-General of WHO introduced IVR in June 1999 at the Montreux Global Vaccine Research Forum. The rationale was to streamline the various vaccine R&D endeavours from different areas of WHO and from UNAIDS, in order to maximize synergies. IVR's mandate is to provide a centralized source of leadership, vision, priority-setting, and coordination with worldwide R&D efforts for the development of vaccines against neglected diseases, particularly in developing countries in which those diseases are endemic. In WHO, IVR is the key body responsible for drawing together the necessary expertise and efforts to address both worldwide priorities, and gaps in capacity, (as well as, where possible, gaps in funding).

IVR facilitates research through prioritization, coordination, and guidance. In addition, three areas that will profit from the linkages provided by IVR to other WHO units are: disease burden studies, capacity-building of National Regulatory Authorities (NRAs), and norms and standard-setting (see the section on "Liaison and networking", below). IVR's R&D activities are cross-sectional, spanning the pipeline from preclinical to post-licensing issues. The disease focus is likewise broad, including platform technologies (such as new delivery systems); global targets (HIV, malaria, tuberculosis); and diseases being treated as a low priority elsewhere (leishmaniasis, Japanese encephalitis, dengue) for example.

As part of WHO, IVR does not compete with other agencies devoted to specific aspects of vaccine R&D; its role is that of a central, over-arching entity, representing the 192 Member States of which it is composed, and thereby occupying a unique position vis-à-vis developing countries.

The mission of IVR is to provide vision, advocacy, coordination, guidance and support to enable the development of safe, effective, affordable and accessible vaccines against infectious diseases of public health importance, especially in developing countries.

The mission of IVR is to provide vision, advocacy, coordination, guidance and support to enable the development of safe, effective, affordable and accessible vaccines against infectious diseases of public health importance, especially in developing countries.

## 1.7 IVR's resource mobilization

IVR activities are financed by WHO's regular budget, UNAIDS, countries' bilateral voluntary contributions, as well as by research contracts and grants. During the 2002–2003 biennium, the governments of Canada, Finland, Japan, Norway, the Netherlands, the United Kingdom and Sweden (in alphabetical order) provided funds for various IVR activities. Funds were also generously provided by the Agence Nationale de Recherches sur le Sida (ANRS), France; the Bill and Melinda Gates Foundation; the Centers for Disease Control and Prevention (CDC), USA; the Global Alliance for Vaccine and Immunization (GAVI); the International AIDS Vaccine Initiative (IVI); the National Institutes of Health (NIH), USA; the Rockefeller Foundation; the United States Agency for International Development (USAID). For global resources for vaccine research and development see also section 2.2 "Key vaccine-oriented international initiatives".

In view of the wide-ranging mission of IVR and its broad portfolio of diseases and activities, additional donors and funds will need to be mobilized in the future.

---

# Part 2:

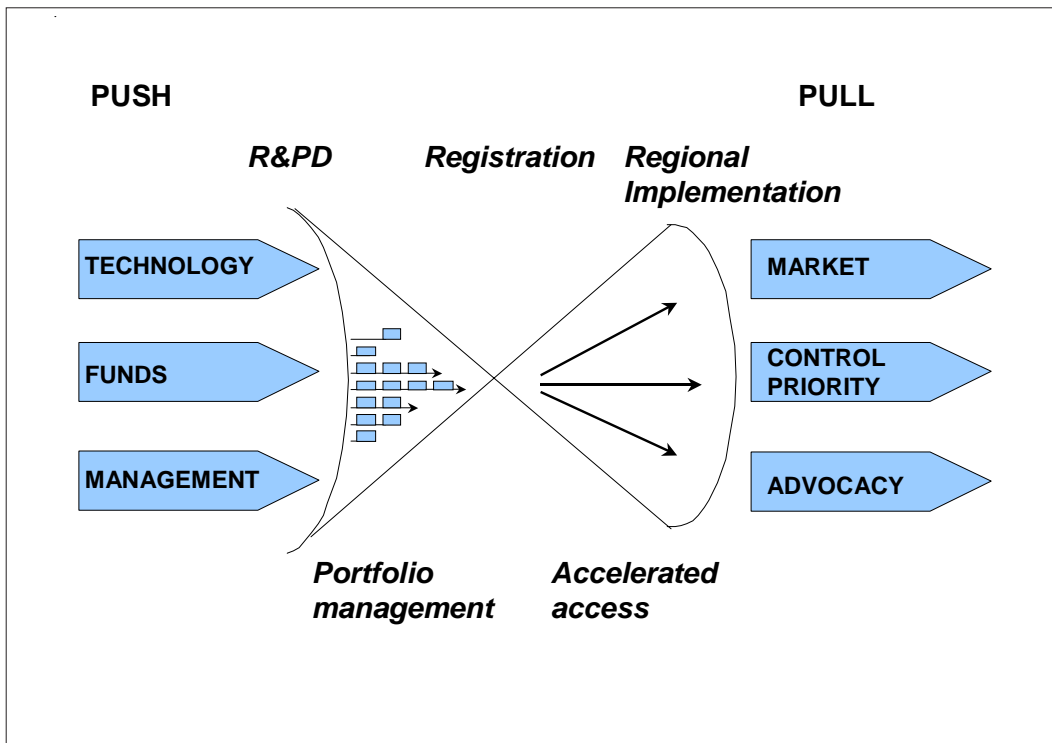
## Driving forces for vaccine research

### 2.1 General driving forces for vaccine research

- In recent years several promising global trends in the public health interventions R&D agenda have occurred:
- Awareness is growing of the fact that health is a prerequisite for economic development;
- The impact of advocacy for ideals of justice and equality for the world's population with regards to health is increasing;
- Both public and private funding has increased for R&D into programmes targeting disease areas relevant to developing countries;
- Several new public and public-private initiatives have been launched.

Several driving forces impact upon the R&D process for public-good targeted vaccine programmes (Fig. 2.1). They can broadly be grouped into two categories, referred to below as “push” and “pull”. Thus, in abstract terms, a product is developed either due to a clear *demand* (a “**pull**”) for the vaccine for which it becomes profitable to *supply* to the marketplace or because it becomes technically feasible (a “**push**”). For vaccines developed by the public sector, the public health needs can act in the same way or supplement demand from the marketplace. In practice, the actual delivery of the product to the population in need is dependent on the concerted action of both “push” and “pull” forces. Within the context of vaccine development, the push forces are principally composed of scientific and technological advances, improvement in management and coordination support structures and availability of product development resources.

**Fig. 2.1:**  
**Driving forces for public health research and product development**



Pull drivers reflect the forces resulting from public health needs and pressure from the marketplace, and derive from the unmet market potential, from national immunization programmes' commitment to procurement and from effective advocacy highlighting the benefit of designating funding to areas with clear unmet medical needs. The investment of resources and efforts in strengthening any of the push and pull forces can affect the product-oriented pipeline. To establish a new pipeline the presence of both forces is required.

## 2.2 Key vaccine-oriented international initiatives

### 2.2.1 Global funding

Governments of many countries provide significant funding for vaccine R&D (see also section 1.7 "IVR's resource mobilization" which details the funds directed specifically to the Initiative). In addition, influxes of funds are channelled to vaccine R&D from various private foundations and nongovernmental organizations, industries or universities.

Effective vaccine R&D relies on efficient management structures with access to long-term committed resources. Several international initiatives and alliances active in vaccine R&D have been created in the past two decades, and especially during the last 10 years. Some of the most important are described below, in chronological

---

order of their establishment, with indications on their objectives, strategic intent and operational model. In addition to these targeted initiatives, many well-established programmes and dedicated international and national institutions provide valuable *ad hoc* support, advocacy and funds for R&D (see the report of the Global Forum for Health Research for a review).<sup>16</sup>

### **UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)**

Officially created in 1975, TDR focuses its activities in two main areas: R&D for new tools (vaccine, drugs, diagnostics, surveillance questionnaires, etc) and strategies and the training of researchers through research capability-strengthening. The set of TDR target diseases comprises malaria, tuberculosis, schistosomiasis, lymphatic filariasis, onchocerciasis, leishmaniasis, American and African trypanosomiasis, dengue and leprosy. To date, although TDR has developed numerous drugs, it has not registered a vaccine. TDR has been promoting a number of malaria vaccine candidates from discovery to advanced preclinical studies and has supported vaccine discovery research for other TDR diseases. TDR's vaccine work has been integrated into IVR (see Part 1).

### **The Program for Appropriate Technology in Health (PATH)**

PATH was established in 1977, with a mission to improve health, and especially the health of women and children in low-resource settings. In 1998, PATH created the Children's Vaccine Program with support from the Bill and Melinda Gates Foundation. Subsequent to that, additional vaccine programmes have been created at PATH including the Malaria Vaccine Initiative, the Meningitis Vaccine Project (in collaboration with WHO), and most recently the Rotavirus Vaccine Program funded by GAVI. PATH is on the Technology Operations Panel that brings WHO, UNICEF, USAID, and PATH together to plan the introduction of new technologies for immunization.

### **The International AIDS Vaccine Initiative (IAVI)**

Formed in 1996 "to assure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world", IAVI is a virtual organization developing vaccines through several "vaccine development partnerships", with an obligatory inclusion of researchers from developing countries. IAVI focuses on the HIV strains prevalent in developing countries. It also supports actions to ensure that future vaccines will be available to all populations in need.

### **The International Vaccine Institute (IVI)**

An international institution established in Seoul, Republic of Korea, in 1997, IVI became fully operational in early 2003. Its aim is "to accelerate the introduction of vaccines into developing country health programmes by undertaking research and providing research-based technical assistance that effectively addresses issues of vaccine development, disease burden, safety and efficacy, delivery feasibility and effectiveness, and sustainable supply". IVI focuses on developing vaccines for diseases

---

<sup>16</sup> *The 10/90 Report on Health Research 2001-2002*, Davey S, ed., Global Forum for Health Research 2002.

---

which result in high morbidity and mortality in Asia; global partnerships; and assistance to private or public programmes to perform field trials in Asia. The projects include a number of enteric, respiratory and vector-borne diseases. A special programme, entitled “Diseases of the Most Impoverished” (DOMI), undertaken in collaboration with WHO, focuses on R&D of vaccines against three diseases: cholera, shigellosis, and typhoid fever.

### **The Children’s Vaccine Program at PATH (CVP)**

CVP was established in 1998 with an initial grant from the Bill and Melinda Gates Foundation. CVP invests in projects to prepare countries for the introduction of new vaccines by gathering scientific information on disease burden, vaccine cost-effectiveness, and immunization delivery. The programme’s R&D efforts currently focus on vaccines against pneumococcus, rotavirus, and Japanese encephalitis.

### **The Malaria Vaccine Initiative (MVI)**

This global programme was established in 1999 through an initial grant to PATH from the Bill and Melinda Gates Foundation. MVI’s mission is to accelerate the development of promising malaria vaccines and to ensure their availability and accessibility for the developing world. MVI’s technical programme supports candidates from laboratory-scale production through to deployment. The main priority is a vaccine to prevent death and severe disease in children. As an integral part of its programme, MVI also undertakes advocacy, business development, and policy activities to support both aspects of its mission.

### **Aeras Global TB Vaccine Foundation**

The Aeras Global Tuberculosis Vaccine Foundation was created in 1997 in response to a critical need for coordination and funding to facilitate the development of tools for tuberculosis control. Working with researchers across the globe, the Foundation intends to be the catalyst for new diagnostics, drugs and vaccines that can stem the rising tide of tuberculosis deaths. In 1999 the Bill and Melinda Gates Foundation awarded the Aeras Global Tuberculosis Vaccine Foundation a grant of US\$25 million over five years to support tuberculosis vaccine R&D. The Aeras Foundation’s focus is mainly on translational research – the under-funded but essential scientific arena between basic research and true product development.

### **The Global Alliance for Vaccines and Immunization (GAVI)**

Established in 2000, the Alliance’s primary aim is “to fulfil the right of every child to be protected against vaccine-preventable diseases of public health concern”. Most of its efforts are concentrated on delivering existing vaccines to millions of children in poor countries and on building up national immunization programmes in these countries. In addition, one of GAVI’s stated objectives is to “accelerate R&D efforts for vaccines needed primarily in developing countries”. IVR is a partner in GAVI, providing technical expertise. Currently GAVI’s R&D priorities are the development of candidate vaccines against meningitis, rotavirus and pneumococcus.

The GAVI R&D efforts for the development and introduction of pneumococcus and rotavirus vaccines have been organized under two programmes described below.

---

### **Pneumococcus Accelerated Development and Introduction Plan (ADIP)**

The Pneumococcus ADIP was awarded to the Johns Hopkins Bloomberg School of Public Health in January 2003 by the GAVI Board. In strategic partnership with WHO, the Pneumococcus ADIP is studying the epidemiology of pneumococcus pneumonia, the prevalence of the *S. pneumoniae* serogroups in developing countries, and evaluating the efficacy of the most advanced conjugate pneumococcus vaccine candidates in developing country settings. The results of these studies will hopefully allow countries and funding agencies to make evidence-based decisions about the introduction of pneumococcus vaccines into childhood vaccination programmes.

### **Rotavirus Vaccine Program (RVP)**

The Rotavirus ADIP was awarded to PATH in January 2003 by the GAVI Board. In partnership with WHO and CDC, RVP is carrying out an accelerated development and introduction plan to deliver a rotavirus vaccine to developing countries. The essential elements of this programme are similar to those of the Pneumococcus ADIP.

### **The Meningitis Vaccine Project (MVP)**

This project is a partnership between WHO and PATH aimed at controlling epidemic meningitis in sub-Saharan Africa through the development, testing, introduction and widespread use of conjugate meningococcal vaccines. The Bill and Melinda Gates Foundation awarded the project, established in 2001, a grant of \$70 million for developing a conjugate meningitis vaccine. Phase I clinical trials of a monovalent A conjugate vaccine tailored for Africa are expected to begin in 2005. The vaccine, when licensed, will have a target price of less than US\$0.50 per dose.

### **The Paediatric Dengue Vaccine Initiative (PDVI)**

A new effort to accelerate the development of a vaccine against dengue was initiated in 2002, with the establishment of the PDVI. The initial development of this Initiative, which was supported by a grant from the Rockefeller Foundation, included the development of research projects to estimate the disease burden of dengue in selected countries in south-east Asia, Latin America and the Caribbean. The PDVI is hosted at the International Vaccine Institute in Seoul, Korea. The Bill and Melinda Gates Foundation awarded the PDVI a grant of US\$56 million in 2003.

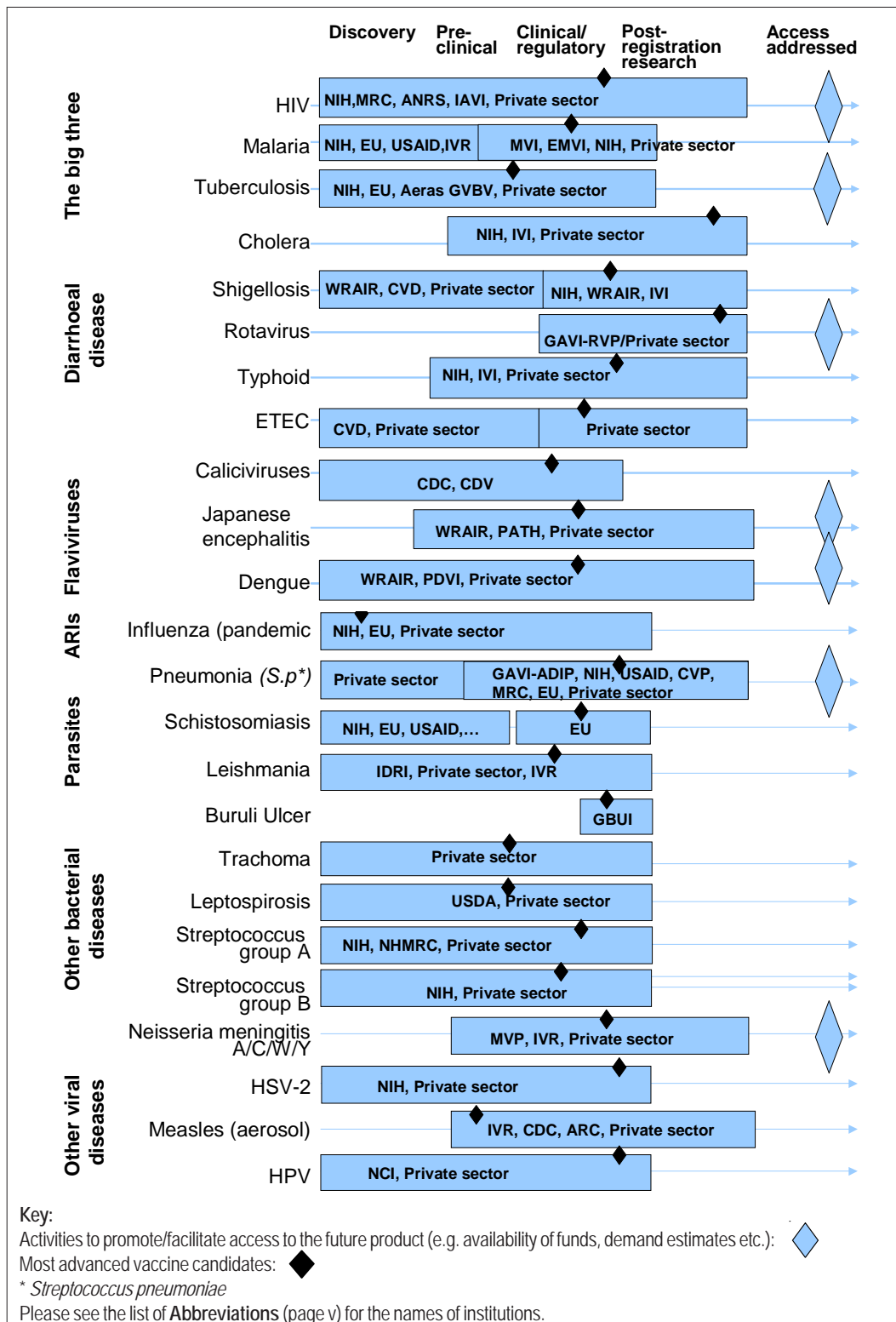
### **The Japanese encephalitis project**

This project was established in 2003, thanks to a grant of US\$27 million awarded to PATH by the Bill and Melinda Gates Foundation, in order to accelerate the development of safe and effective vaccines against Japanese encephalitis.

In summary, the group of institutions and initiatives that intend to work on vaccine development and supply have very diverse mandates, modes of operation and target disease priorities. Most of the more recent initiatives have understandably no track record of achievements yet and are often supported by short-term and non-binding resource commitments. In spite of an increasing number of players working towards a common goal of elaborating global public-good vaccines, their stated roles are sometimes fragmented and the global vaccine development pipeline (illustrated in Fig. 2.2 below) reflects this fact. The pipeline still does not cover all the essential aspects of the vaccine development continuum. These aspects include discovery, preclinical research, clinical/regulatory and post-licensing research, and access to

vaccines for all infectious diseases of public health importance. Ideally therefore, public sector players in vaccine R&D should attempt to fill the gaps that have been identified. The best way to achieve this would be through active collaboration, where all partners work for the common good without too much competition.

Fig. 2.2: The global vaccine R&D pipeline



---

### 2.2.2 *IVR vision*

IVR's vision is: **“To develop and promote a global and sustainable R&D pipeline delivering the optimal vaccines for WHO vaccine R&D priority diseases.”** This in line with the long-term vision of the WHO Department of Immunization, Vaccines and Biologicals, which is “A world in which all people at risk are protected against vaccine-preventable diseases”.

To achieve this IVR focusses on critical steps, leveraging existing research, development and management opportunities, and proactively identifies and promotes a set of targets for each stage of development (see part 4). While developing vaccines, IVR works to ensure that candidate vaccines are as cost-effective as possible, so as to facilitate access to those vaccines in the future by developing countries.

### 2.2.3 *IVR comparative advantages*

- IVR is an international team made up of highly qualified project managers, scientists and public health and technical experts selected, through a highly competitive process, from a diverse national and cultural background. The breadth of in-house technical expertise related to vaccine R&D therefore crosses many disciplines, from basic science to product R&D and vaccine introduction.
- IVR has a portfolio of ongoing projects with established teams and partnerships. Through its convening power IVR can call together all relevant parties, including the private sector, to reach for consensus on R&D priorities, and to engage them in projects and initiatives, drawing on their knowledge and expertise in disease control, as well as in regulatory and policy matters. Once those challenges have been identified, IVR can mount an appropriate response to them with the help of its advisory bodies (Steering and Advisory Committees) and governing structures representing a wide global constituency, and using different mechanisms depending on the particular issue.
- IVR works in close association with WHO units and initiatives like the Stop TB and Roll Back Malaria partnerships, or with UNAIDS or GAVI. These partners have knowledge and expertise in disease control, as well as in regulatory and policy matters. Wide-scale implementation of new vaccination strategies is ensured through the use of the WHO global network of six regional offices.
- As part of WHO, which is the United Nation's specialized agency for health, IVR is able to integrate the vaccine research and development process into the global health agenda. IVR is independent in its opinions and judgements and free from commercial or national influences or lobbying. In its trusted capacity as the “impartial broker” IVR can coordinate processes among partners and communities. It is a powerful advocate for developing countries' needs and can also provide management support for the fostering of new initiatives. IVR has both the mandate and the capability to bridge North and South, as well as South with South, and to engage in research capacity-strengthening and policy development.

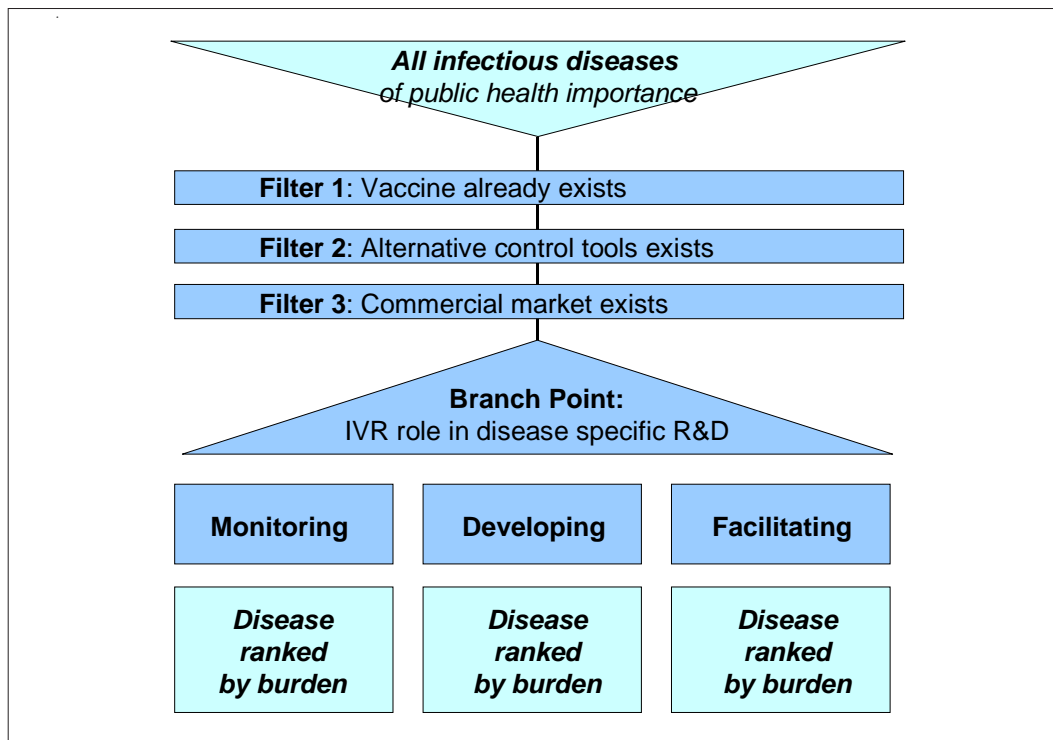
# Part 3:

## Priority setting

### 3.1 Priority-setting

Resources are always limited – for both public and private sectors. The limitation on funds, researchers, and management efforts together with a variety of technical, ethical and political criteria, which are always modifiable in the light of new data or perceptions, make it essential to prioritize on a quantifiable basis. IVR’s framework for setting disease and activity priorities in research and vaccine development therefore needs to be evidence-based and to remain very flexible (Fig. 3.1).

Fig. 3.1: The decision tree for IVR priority-setting framework



---

### 3.1.1 *The framework*

The starting point for the prioritization process is “all infectious diseases of public health importance”. Several criteria are then applied to this group. For example, WHO’s commitment to reach measles mortality-reduction objectives means that measles vaccine R&D is a high priority even though an effective inexpensive vaccine against measles exists.<sup>17</sup> However, a vaccine against African trypanosomiasis is not included in the IVR disease portfolio, on the grounds of a comprehensive analysis conducted by TDR and endorsed by TDR’s governing bodies. Three *filters* are subsequently used to select IVR target infectious diseases. These filters eliminate (from the vaccine R&D portfolio) diseases which already have either:

- effective vaccines widely available, or
- sufficient alternative treatment tools that could be fully implemented for control of the diseases, or
- which represent a sufficiently attractive commercial proposition for new vaccine development and deployment in developing countries.

The choice of filter criteria follows the generalized logic widely employed by public health agencies investing in vaccine research and development.<sup>18</sup> Further on at the decision tree “branch point”, illustrated in Fig. 3.1 above, the diseases are categorized according to which IVR activity will be most beneficial: (“developing”, “facilitating” or “watchful waiting”).

In order to reflect the evolving environment, this prioritization is reviewed each year.

---

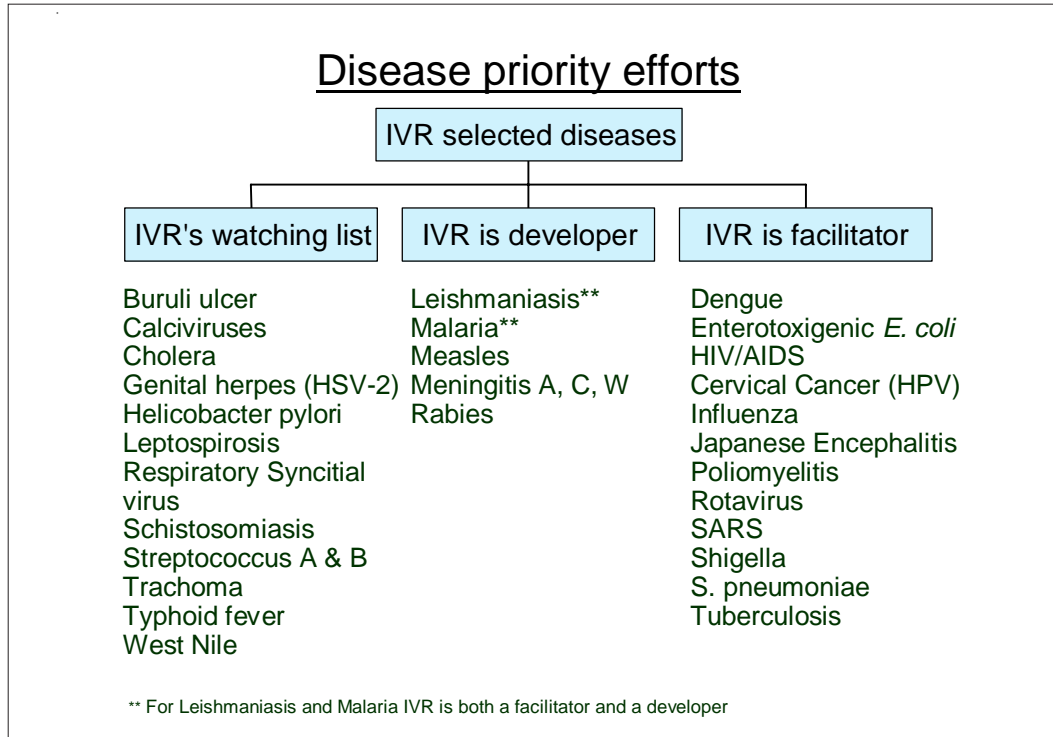
<sup>17</sup> The World Health Organization’s commitment in World Health Assembly resolution WHA56.20 “Reducing global measles mortality” in May 2003 reflects the objectives set by the United Nations Assembly Special Session on Children in 2002 and the United Nations Millennium Development Declaration.

<sup>18</sup> <http://www.brookings.edu/comm/policybriefs/pb57.htm>

### 3.1.2 Three types of involvement for IVR

IVR's current disease priority clusters can best be illustrated in Fig. 3.3 below.

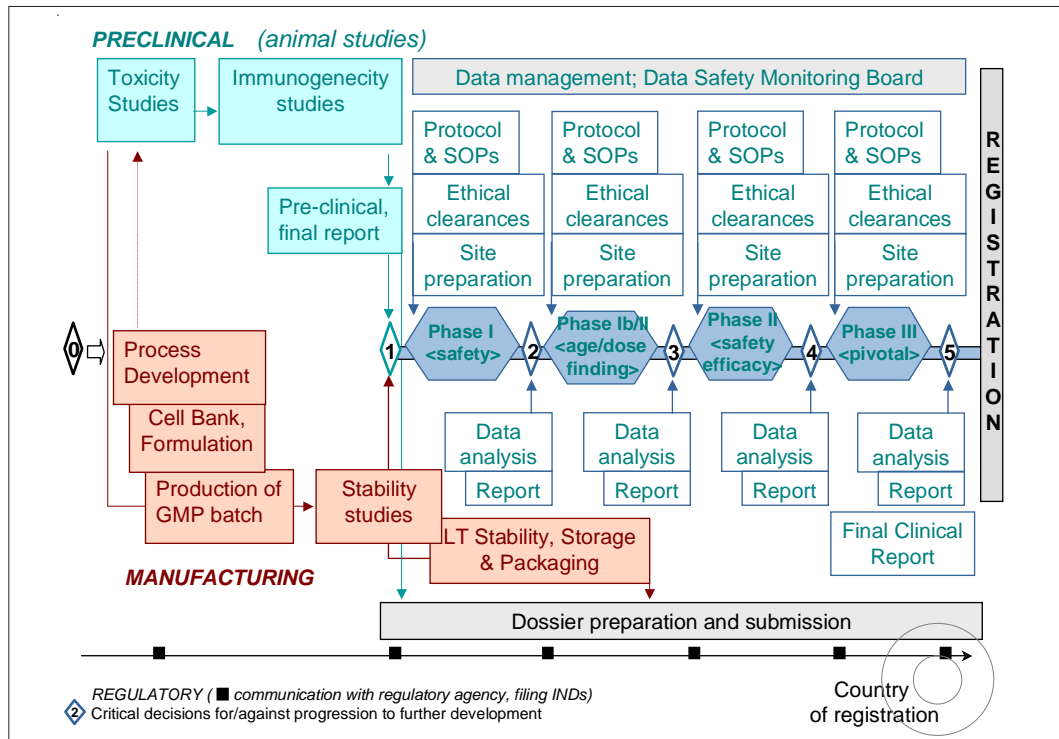
Fig. 3.2: IVR disease priority efforts



IVR's role is as “*developer*”, where the vaccines to be developed (like measles aerosol vaccine) lack private and public R&D investment, and where a more active role of WHO in product development will benefit the disease-specific pipelines.

IVR adds its strengths to specific development projects, directly supporting some of the associated research and management tasks, and forging the appropriate partnerships and co-sponsorship relationships to support others. A schematic vaccine research and product development process is outlined in Fig. 3.3 below. IVR can become involved at any of the points in this process.

Fig. 3.3: The vaccine research and product development process



For vaccines for which IVR is a “*developer*”, a “virtual” development team driving product development and licensing for the developing-country market is established. This team is funded by the public sector and is a non-profit exercise. It operates in cases where a potential manufacturer is not taking full responsibility for the development/licensing of a new product or of tailor-made vaccines specifically targeting the population of a region.

All development projects involving collaboration with IVR partners are subject to a memorandum of understanding (MOU) or to other agreements assuring accountability, high ethical standards and the securing of preferential pricing of vaccines for developing countries.

IVR engages in a “*facilitator*” type of role for the group of priority diseases, like HIV/AIDS, tuberculosis or dengue, where there are significant numbers of funding agencies and managerial product development programmes or support structures along the whole vaccine pipeline of R&D. In this situation IVR does not attempt to sponsor the development of specific vaccine candidates but proposes to partners that it should facilitate the ongoing global research and product development and play the role of independent, objective process consultant and strategic or technical adviser (see Box 3.1 below). In terms of financial involvement, IVR provides seed funds, bridging support, or resources to fill funding gaps for these diseases.

---

### Box 3.1: How IVR facilitates the R&D process

A number of mechanisms are considered to accelerate the R&D of vaccines of public health importance. Several supporting mechanisms could be put into place on a case-by-case basis to harmonize the global research agenda and to facilitate product development:

- Proactively identifying and bridging research gaps
- Discovering and evaluating disease animal models and *in vitro* assays for preclinical research
- Validating commonly accepted vaccine evaluation criteria and target product profiles
- Participating in the harmonization of internationally accepted quality standards and the regulatory requirements used in vaccine research and development
- Facilitating the establishment and monitoring of clinical trial sites for vaccine evaluation in developing countries
- Linking product development with implementation and operational research early in the product development cycle
- Consulting with the control programmes of disease-endemic countries
- Advocating for and initiating effectiveness studies of intervention in various epidemiological settings
- Conducting cost analysis to advocate for global/regional vaccine introduction

In some instances, while being “facilitator”, IVR may host individual development projects, for example on the recommendation of the IVR Advisory Committee or of a disease-specific international steering committee, provided that the project is fully supported by designated funds with appropriate human resources. These projects, while being a part of IVR, are considered to be independent from, and subsidiary to, other activities facilitating product-development.

Diseases like schistosomiasis are held in IVR’s R&D “*watchful waiting*” cluster because research into this cluster is currently perceived to have a lower impact than elsewhere in terms of global health benefit, and the costs and technological risks associated with R&D are seen to be too high.

Diseases move through the priority list, as the global vaccine R&D pipeline develops, and partnerships strengthen, either by being “filtered” or by moving from the “watchful waiting” list to the “developing” and “facilitating” clusters if an opportunity for research and/or partnership should arise.

Table 3.1 below indicates how priorities were set for IVR for the period 2004–2005.

Table 3.1: Working table for IVR priorities

Disease or infectious agent	Epidemiology		Filter 1	Filter 2	Filter 3	Branch Point	Rank	IVR unit(s)
	DALYs ('000) (a)	Estimated number of cases/deaths for 2002 when DALYs are not available ('000)	Vaccine sufficient for control exists	Alternative treatment sufficient for control exists	Sufficient resources and efforts to develop vaccines for global needs, low IVR added value	IVR's Role: Facilitator-Developer-Watching	Global, Regional disease	IVR responsible unit
<b>Three biggest killers</b>								
HIV/AIDS	86072					F	G	HVI
Tuberculosis	35361					F	G	BAC
Malaria	44716					F/D	G	POP
<b>Diarrheal Diseases</b>	61095							
Cholera		137000/4900				W	R	BAC
Shigella		200000/1100				F	R	BAC
Enterotoxigenic Escherichia coli		400000/700			Targeted by GAVI	F	G	BAC
Rotavirus		125000/600				F	G	BAC
Typhoid		16000/600				W	R	BAC
Caliciviruses		1-1000/100-500				W	R	BAC
<b>Acute Respiratory Infections</b>	90252							
Haemophilus influenzae type B (Hib)		3-5000/4-700	X (b)					
Streptococcus pneumoniae		10-100000/1000			Targeted by GAVI	F	G	POP
Respiratory Syncytial Virus		64000/160				W	G	POP
Para Influenza Virus type 3		>10000/10-100			X (c)			
Influenza virus		1 million/200-500	According to WHO prioritization			F	G	POP
SARS		8/-1				F	R	POP
<b>Childhood diseases (EPI)</b>	49844							
Pertussis	13052		X (b)					
Poliomyelitis	152		According to WHO prioritization			F	G	POP
Diphtheria	184		X (b)					
Measles	27058		According to WHO prioritization			D	G	BAC
Rubella		>100/?	X (b)					
Mumps		1 million/?	X (b)					
Tetanus	9398		X (b)					
<b>Infections contributing to cancer burden</b>								
Helicobacter pylori		?/744				W	G	BAC
Human Papilloma Virus		?/288				F	G	BAC
<b>STI (excluding HIV)</b>								
Syphilis	4200			X (d)				
Chlamydia	3571			X (d)				
Gonorrhoea	3365			X (d)				
<b>Meningitis</b>	6195							
Meningitis A, C, W		300/25-30				D	R	BAC
Meningitis B		20-80/2			X (e)			

continued/...

**Table 3.1: Working table for IVR priorities (continued)**

Disease or infectious agent	Epidemiology		Filter 1	Filter 2	Filter 3	Branch Point	Rank	IVR unit(s)
List of diseases or corresponding infectious agents grouped according to...	DALYs ('000) (a)	Estimated number of cases/deaths for 2002 when DALYs are not available ('000)	Vaccine sufficient for control exists	Alternative treatment sufficient for control exists	Sufficient resources and efforts to develop vaccines for global needs, low IVR added value	IVR's Role: Facilitator-Developer-Watching	Global, Regional disease	IVR responsible unit
<b>Tropical diseases (excluding TB, dengue &amp; Malaria)</b>	12454							
Leishmaniasis	2090					D	R	POP
African trypanosomiasis	1535		According to TDR's strategic matrix (k)			W	R	POP
Schistosomiasis	1702							
Chagas diseases	667							
Lymphatic filariasis	5777							
Oncocerciasis	484							
Leprosy	199							
<b>Other viral diseases</b>								
Hepatitis B	2177		X (f)					
Hepatitis C	1001				X (g)			
Hepatitis E		100-1000/<10			X (h)			
Rabies		>7000 PET/50-60	Immunoglobulins			D	R	POP
Dengue	616		According to TDR's strategic matrix (k)				F	RPOP
Japanese Encephalitis	709					F	R	POP
West Nile						W	R	POP
Tick Borne encephalitis			X (i)					
Herpes Simplex Virus type 2		600/10-100				W	G	HVI
Epstein Barr Virus		<100/<10			X (j)			
<b>Other bacterial diseases</b>								
Trachoma (blindness)	2329					W	R	BAC
Streptococcus A						W	G	POP
Streptococcus B						W	G	POP
Leptospirosis						W	G	BAC
Buruli Ulcer		>200/?				W	R	BAC

- (a) *The World Health Report 2003: Shaping the future*. Geneva, World Health Organization, 2003.
- (b) Pertussis, diphtheria, tetanus, Hib, rubella, mumps: effective (cheap) vaccines delivered with the Expanded Programme on Immunization (EPI)
- (c) PIV-3: high level of investment from industrialized country manufacturers; no vaccine available for accelerated introduction in developing countries
- (d) Syphilis, chlamydia, gonorrhoea: antibiotic treatment effective
- (e) Meningitis B: high level of investment from industrialized manufacturers
- (f) Hepatitis B: effective cheap vaccine available
- (g) Hepatitis C: high level of investment from industrialized manufacturers; science not mature enough
- (h) Hepatitis E: sufficient investment from industrialized manufacturers; no vaccine available for accelerated introduction in developing countries
- (i) Tick-borne Encephalitis: cost-effective vaccine available
- (j) Epstein Barr virus: sufficient investment from industrialized manufacturers; no vaccine available for accelerated introduction in developing countries
- (k) TDR Strategic Emphases Matrix, October 2002, <http://www.who.int/tdr/grants/strategic-emphases/files/matrix.pdf>

The detailed explanation for why each of the selected diseases has been categorized into the “facilitator”, “developer” or “watchful waiting” categories is summarized in Annex 1.

---

## 3.2 Support for vaccine R&D technology and practices

IVR's activities affect the general formation of push and pull driving forces (Technology, Funds, Management, Advocacy, Control priorities, Exploring the market; see Fig. 2.1 "Driving Forces for public health research and product development") and thereby contribute to and influence the new vaccine pipeline.

### 3.2.1 Technology

IVR supports research on platform technologies and on basic research which focuses on removing or lowering technological hurdles: finding surrogate markers and clinical end-points, choosing adjuvants, accessing pilot lot production facilities and novel delivery systems etc.

IVR provides significant input to several cross-cutting areas, including:

- support to new platform *technologies* and new delivery systems to improve immunization;
- assessment of common issues in *clinical trials*, such as clinical site identification and development, or setting up of good clinical practice training and capacity-building in general;
- identification of *ethical issues*, clearance of protocols and training;
- support for *technology transfer* through technical expert consultation and provision of advice in production matters;
- *generation of databases of useful information*, such as contract manufacturers for pilot lot production or clinical trial sites;
- analysis of a number of subjects related to *immunization strategies*, such as different immunization schedules, or vaccination of immuno-compromised and special groups;
- *information and knowledge management* for vaccine R&D: websites, publications, best practices templates, promoting training and information materials on vaccine R&D processes for developing countries.

Within the above cross-cutting areas, IVR activities in the domains of new delivery systems, clinical trial-related activities, research capacity-building and ethical training are briefly outlined in the three boxes below.

---

### **Box 3.2: Novel delivery systems**

The problem of access to vaccines is partly caused by logistical difficulties associated with the need to refrigerate vaccines during transport and storage. Several technologies are under development which could make vaccine delivery independent of the cold chain by producing vaccine stability at temperatures significantly higher or lower than typical refrigeration temperatures.

Safety is another issue associated with vaccine delivery. Re-use of needles and syringes and unsafe injection practices are estimated to cause an high number of infections.

Alternative routes of vaccine administration, through the mucosal (oral and nasal) and transcutaneous routes, would thus significantly increase the safety of vaccine delivery. In addition, such technologies would simplify the logistics of immunization and possibly reduce its cost. As a result, coverage could be considerably increased. Globally, significant efforts are focused on developing technologies to improve immunization services. Within IVR, a separate area of work (NDS) has been established to coordinate these efforts and to identify and promote research that could improve the coverage, safety and logistics of vaccination. Three categories are the focus of special attention: vaccine stabilization, needle-free immunization and delivery devices.

### **Box 3.3: Activities related to clinical trials and research capacity-building**

#### *Clinical trials*

IVR is involved in activities relating to the clinical evaluation of various new vaccines, either as facilitator or as sponsor of clinical trials. Related activities include development of protocols and of other documents i.e. sponsor's file, monitor's file and investigator's file, submission to ethical committees/IRB, selection of clinical trial sites/principal investigators, participation in Data Safety Monitoring Boards, monitoring of clinical trials and analysis of trial results/reports.

#### *Research capacity building*

If required, IVR can provide support for research capacity-building to potential investigators and sites in accordance with the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) and WHO good clinical practice guidelines to ensure the quality of future clinical trials.

---

### Box 3.4: Ethics training

In recent years, the increasingly global nature of health research, and in particular the conduct of clinical trials involving human participants, has highlighted a number of ethical issues, especially in those situations where researchers or research sponsors from one country wish to conduct research in another country. IVR emphasizes training and capacity-building in research ethics. For this it is necessary to consider:

- Targeted short-term training courses and workshops, linked to specific research needs and projects, contributing both to individual and to institutional capacity-building.
- The participation of developing-country scientists in the conduct of phase I/II vaccine trials in industrialized countries, which should be encouraged as an integral part of their training.
- Onsite training, or South-South training, must be explored. Eventually, developing-country academic institutions could develop specific training curricula to satisfy their own long-term training needs.

#### 3.2.2 Funds

Although IVR is not primarily a funding agency, the Initiative provides seed funds or bridging financing grants for development projects, and small grants for basic research and developing platform technologies as recommended by the IVR steering committees. IVR meets some of the funding requirements for projects where it has a “developer” role. In most cases this is done in partnership with other agencies or groups.

#### 3.2.3 Management

IVR manages both individual projects and the overall IVR project portfolio, proactively promoting development and facilitating research and clinical trials of collaborating parties, ensuring ethics and good preclinical and clinical practices for individual projects. IVR participates in building the global pipeline and network for vaccine research on neglected diseases. Through these activities, IVR is a member of other initiatives and participates in the work of other committees, expert meetings, and portfolio evaluation reviews. In addition, IVR has *ad hoc* involvement in external projects aligned with IVR priorities. The Initiative acts as a catalyst for public-private partnerships or cross-public partnerships to manufacture and distribute developed vaccines. Importantly, IVR is responsible for launching and fostering new regional initiatives, like the African AIDS Vaccine Programme. Whenever feasible, IVR invests in project-based research capacity-strengthening.

#### 3.2.4 Advocacy

IVR determines the WHO agenda on vaccine research and participates in setting the global public health agenda. By linking to the disease-control programmes of developing countries, IVR can be an advocate of the public health agenda in vaccine research.

---

### Box 3.5: Advocacy for HIV vaccines

IVR is a powerful advocate of developing countries' needs. An example is provided by the role of IVR in promoting the development and evaluation of HIV vaccines in association with the recently launched African AIDS Vaccine Programme sponsored by WHO/UNAIDS.

Although 95% of all HIV infections occur in developing countries, not enough is being done to develop candidate vaccines based on the HIV subtypes prevalent in these countries. Likewise, more clinical trials need to be conducted in developing countries to accelerate the availability of **information** related to the potential protective efficacy of different vaccine concepts to prevent infections with different HIV subtypes and in populations which may differ in the route of transmission of the virus, genetic background, or nutritional or health status.

#### 3.2.5 *Control priorities*

IVR's links to disease-control programmes and other upstream public sector entities which determine priorities for interventions against infectious diseases and provide control programmes with news of the latest vaccine R&D. Through these communication channels, early implementation issues can be addressed in a timely manner, and distribution channels adapted to future needs.

#### 3.2.6 *Exploring the market*

IVR has links with epidemiological, health-economic and social marketing research to forecast vaccine demand. Contacts are also established with public health agencies hosting funds dedicated for purchasing vaccines for developing countries. An example of such an agency initiative is that of the World Bank which has discussed the possibility of establishing a World Bank vaccine purchasing fund which could provide up to US\$400 million a year in credits to countries purchasing vaccines for malaria, tuberculosis and HIV/AIDS, when they become available.<sup>19</sup> Although this idea has not been implemented up to now, a commitment was made, that up to \$1000 million in resources would be available to help any International Development Association (IDA) or International Bank for Reconstruction and Development (IBRD) country wishing to purchase an effective HIV/AIDS vaccine once one became available. The World Bank has since taken a new approach of piloting "investment partnerships" in which a third party like the Bill and Melinda Gates Foundation earmarks funds to "buy-down" the cost of a loan or credit for a project with global public-good characteristics, as immunization/vaccine projects often are.

Cost-effectiveness analyses can be used to guide policy decisions. Rather than supporting a policy decision merely because it appears to be effective or because it enjoys political support, systematic analysis enables policy-makers to determine whether a policy decision reflects the best use of available resources.

IVR is increasingly undertaking cost-effectiveness analyses in order to make best use of its own resources and to advise partners on the best use of their investments.

---

<sup>19</sup> Immunization, Vaccines and Biologicals, Strategic Plan 2002-2005. World Health Organization, Geneva, March 2003. WHO/V&B/02.02

---

# Part 4:

## IVR strategic plan 2004–2005

### 4.1 Objectives and milestones

This IVR Strategic Plan, 2004–2005, fits practically and conceptually within WHO's Immunization, Vaccines and Biologicals (IVB) 2002–2005 Strategy.<sup>20</sup> The IVR Strategic Plan describes the current work and future direction of the Initiative, grouped under four of the nine IVB targets. Each target is associated with an indicator against which progress is measured and each names a number of products that need to be delivered. The emphasis in IVR's mandate is most clearly reflected in targets one and two of the IVB strategy which are to: **“discover new candidate vaccines and delivery methods, and evaluate the proof of principle of their efficacy”** and **“facilitate late-stage clinical development of appropriate formulations of new vaccines into disease-endemic developing countries”** respectively.

IVR also collaborates with other IVB teams on the fulfilment of IVB's target eight, to **“certify all WHO regions as polio-free in 2005”** and target nine, to **“reduce measles mortality and achieve regional elimination goals”**.

Over IVR's Strategic Plan timeframe, significant progress in implementation is measured by the milestones accomplished. This structure links directly to WHO's principal financial planning tool – the Programme Budget – which reflects the same objectives and expected results on a biennial basis, and illustrates the allocation of WHO's financial resources by geographical area.

An updated version of the IVR Strategic Plan will be produced at the end of 2005 for the period 2006–2008, concomitant with the production of an updated version of the IVB strategy.

---

<sup>20</sup> Immunization, Vaccines and Biologicals, Strategic Plan 2002–2005. World Health Organization, Geneva, March 2003. WHO/V&B/02.02

---

# Target one

---

## IVR Target

Discover new candidate vaccines and delivery methods, and evaluate the proof of principle of their efficacy.

## Expected Result

Research and development promoted and preclinical evaluation facilitated for new candidate vaccines against tuberculosis, malaria, shigellosis and dengue (in collaboration with the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases) and HIV/AIDS (in collaboration with UNAIDS).

## Critical Indicators

1. Number of WHO-supported vaccine candidates advancing from preclinical to clinical evaluation or progressing in the phase of clinical evaluation
2. Proportion of WHO support for vaccine research and development allocated to studies in developing countries

## Status

Globally, the development of new vaccines is a complex and expensive process that involves many partners in both the public and private sectors. In budgetary terms, WHO is only a minor player in vaccine R&D, as compared to classical research funding agencies, philanthropic organizations and the vaccine industry. Nevertheless, in a field that is largely driven by expectations of significant economic returns on the one hand and by academia on the other, WHO has an important role to play: assuring that at least a significant part of the vaccine R&D effort is directed towards the development of safe, effective and affordable vaccines for use in developing countries.

In accordance with the different nature of these hurdles, WHO has developed, together with international partners, a specific R&D agenda, tailor-made for each pathogen in order to remove obstacles and thus accelerate the availability of the final products. These global agendas clearly identify areas of WHO's comparative advantage. Examples in the preclinical area include in particular: filling knowledge gaps through targeted research projects; the establishment of networks for preclinical evaluation of vaccine candidates under standard conditions; the preparation of guidelines; and the provision of reference reagents and clinical isolates.

Table 4.1 represents, in broad terms, the global state of development of each vaccine type at the end of 2003, and indicates the predominant area of activities for each product. The research and development of vaccines can include various candidates for the same product in different development phases at any given time. The table reflects the primary targets of IVR's activities (diseases for which the IVR strategy consists of playing the role of facilitator or developer, as well as cross-cutting technical areas).

**Table 4.1: Predominant areas of activity for Target 1**

Product	Standardization	Epidemiology	Discovery	Preclinical studies	Phase I	Phase II
Global activities P1 Tuberculosis IVR activities	+	+	+	+	+	+
Global activities P2 Shigellosis IVR activities	+	+	+	+	+	+
Global activities P3 Dengue IVR activities	+	+	+	+	+	+
Global activities P4 Acute resp. inf. IVR activities	+	+	+	+	+	+
Global activities P5 NDS IVR activities	+		+	+	+	+
Global activities P6 Malaria IVR activities	+	+	+	+	+	+
Global activities P7 Leishmaniasis IVR activities		+	+	+	+	
Global activities P8 Rabies IgG IVR activities		+				

Note: NDS novel delivery systems  
(+) provided funding available

## 1.1 Tuberculosis vaccine

### Purpose

To accelerate the development of an improved vaccine against tuberculosis.

### Context

Despite substantial international efforts to treat active cases chemotherapeutically and to immunize against the disease using the BCG vaccine, tuberculosis continues to create an overwhelming disease burden in many global communities. It causes about 8 million new cases every year and is one of the leading infectious causes of death worldwide. One-third of the world's population is infected with *Mycobacterium tuberculosis* rising to two-thirds in certain geographic areas, such as Africa, where 25% to 75% of people infected with the tuberculosis bacillus are also HIV-positive, this being the single most important risk factor for infection to develop into clinical disease. Tuberculosis not only affects public health in these communities but also has a major impact on society and on the economy, especially of developing nations. The BCG vaccine, although it is efficacious against extra-pulmonary complications of tuberculosis in children, is highly variable in its protective efficacy against pulmonary disease, the main problem in adolescents and adults.

---

## Status

Substantial progress in genomics and proteomics, immunology and the vaccinology of tuberculosis has been made in the last years. This has resulted in the development of prospective vaccine candidates against tuberculosis including live, adjuvanted subunit, DNA, rationally attenuated *M. tuberculosis* and “improved BCG” that have shown promise in preclinical studies. One of these candidates has entered into human clinical studies and several more are likely to follow in the near future. WHO acts as facilitator in the area of R&D for vaccines against tuberculosis and provides support to the vaccine development process through advocacy, normative support (guidelines, physical standards/reagents, etc.) epidemiological back-up, health-economic analysis, site identification/ characterization, and capacity-building for infrastructure/research.

## Milestones

In 2004:

- The TB vaccine resources website goes live.
- A monograph on animal models for TB vaccine evaluation is published.
- At least one immunological indicator of vaccine-mediated protection against TB is standardized.
- Guidelines for phase I and II clinical investigation of a vaccine against TB are published and a directory of potential sites for phase III trials is developed.
- A TB vaccine impact model is developed and published.

In 2005:

- Two clinical sites are ready to start phase III efficacy testing of a new candidate vaccine against TB. (WHO contribution: strengthening capacity by training and provision of methodology and assays)
- Updated guidelines for BCG characterization are published.
- Two phase I/II clinical trials of a vaccine against TB are completed. (WHO contribution: provision of protocols, training and capacity strengthening)
- A health economic study for the development of a vaccine against TB is published.

### 1.2 *Shigella* vaccines

#### Purpose

To accelerate development of new parenteral and oral vaccines against *Shigella* infection.

#### Context

It has been estimated that more than 163 million episodes of endemic shigellosis occur each year in developing countries. Over 1 million of these cases are fatal. In developing countries, the major burden of *Shigella* infection is among children

---

less than five years of age. There is room for optimism, however, as advances in biotechnology have enabled research institutions in the public sector to develop a new generation of candidate vaccines that show great promise for the prevention of shigellosis. However, no manufacturer is currently developing a vaccine against this pathogen. The public sector needs to give special attention to this “orphan” vaccine, establishing some sort of partnership to accelerate its availability and introduction in developing countries.

## Status

There are two principal approaches in the development of vaccines against shigellosis: (i) subunit vaccines based on either conjugates containing the O-specific polysaccharide of *Shigella* lypopolysaccharide (LPS) or ribosomes extracted from atoxic lipid A *Shigella* strains, in collaboration with the programme against diseases of the most impoverished (DOMI); and (ii) live bacteria with genetically engineered mutations in a virulence gene and/or a synthetic pathway gene. For example, an oral live attenuated candidate (SC602) has already been evaluated in phase I and II trials with volunteers in North America and in Bangladesh and a phase III trial will be undertaken in a developing country setting, monitored by WHO through participation in the Data Safety and Monitoring Board.

## Milestones

In 2004:

- An international technical meeting is organized on the “*Future Needs for Shigella Vaccine Research for Children in Developing Countries*”. The meeting report serves as the agenda to focus research activities during the next three to five year period for Shigella vaccines.
- Surveillance activities for Shigella burden of disease are initiated in sub-Saharan Africa.
- Surveillance activities and translational studies are ongoing in Asia. (WHO contribution: technical assistance with limited funding support; IVI to co-ordinate and fund activities)
- A live oral attenuated multivalent vaccine is evaluated in a phase I/II trial. (WHO contribution: technical assistance and funding support; the Center for Vaccine Development (CVD), Maryland, USA will co-ordinate the trial)

In 2005:

- A live oral attenuated multivalent Shigella vaccine phase II clinical trial is ongoing. (WHO contribution: technical assistance and possible partial support; CVD will co-ordinate the trial)
- A phase III trial of an oral live attenuated candidate vaccine (SC602) is ongoing in a developing country. (WHO contribution: technical assistance, IVI will co-ordinate the trial)
- Studies to identify distribution of antibiotic resistance of circulating Shigella strains are ongoing in some developing countries. (WHO contribution: to facilitate and offer technical/funding assistance)

---

### 1.3 Dengue vaccine

#### Purpose

To promote the development of safe and effective vaccines against all four dengue serotypes to reduce the risk of acquiring dengue haemorrhagic fever.

#### Context

Every year, 50 million people throughout the world are affected by dengue fever or the more serious dengue haemorrhagic fever (to which children are especially vulnerable), which can lead to shock syndrome and death. Each year, more than half a million people are hospitalized and approximately 30 000 die from this disease. As there is no drug to cure dengue, and the prevention of human disease by vector control is impractical, immunization is a key control measure.

#### Status

An immense array of possibilities for vaccine development opened up with the sequencing of the flavivirus genome during the 1980s along with the identification of the genes encoding the proteins relevant for eliciting an immune response. Dengue vaccine development has focused on two main approaches. The first is the serial passaging of a virus in tissue culture (or animal tissues) and examination of viral properties at specific passage levels. The second approach uses different biotechnological techniques including recombinant and subunit vaccines, DNA and infectious clone technologies. Over the period of this Strategic Plan, WHO will provide scientific advice and technical support to some phase I/II clinical trials of vaccines against dengue. Criteria for safety “follow-up” of dengue vaccines will be developed.

#### Milestones

In 2004:

- A standardized protocol is developed for evaluation of vaccines against dengue in monkeys. (WHO contribution: funding to the project)
- Studies are completed on the mechanism of immune enhancement and neutralization escape. (WHO contribution: support to selected research projects)

In 2005:

- A cohort is prepared for phase III trials of tetravalent dengue vaccine in a developing country. (WHO contribution: technical advice)
- Criteria to assess long-term safety will be developed.

---

## 1.4 Vaccines against acute viral respiratory infections

### Purpose

To accelerate the development and evaluation of novel candidate vaccines against influenza and SARS.

### Context

Viruses are a common cause of acute lower respiratory infection in children worldwide. Nearly one million deaths occur every year due to influenza virus infections, and many millions could die in the event of a future pandemic.

The recent identification of a new coronavirus (CoV) as the etiological agent of the Severe Acute Respiratory Syndrome (SARS) is another example of an emerging disease, the control of which may require a vaccine. During the 2002–2003 outbreak, the SARS CoV has caused more than 8000 cases of SARS, among which nearly 800 were fatal.

### Status

Safe and effective influenza vaccine exists, based on two envelope viral proteins: haemagglutinin and neuraminidase. The protection afforded by these vaccines is usually very narrow, and new vaccines must be produced in the case of even minor antigenic variations caused by point mutations (*antigenic drift*). IVR is exploring the feasibility of developing a new generation of influenza vaccines that could be more appropriate to confront the threat of future pandemics (caused by major antigenic changes (*antigenic shift*)). This includes vaccines that are more broadly protective and that confer longer-lasting protection.

IVR will monitor the SARS epidemiological situation and explore ways to facilitate the possible development of a vaccine. IVR will ensure that, once developed, that vaccine is available for use in developing countries. One area of activity involves facilitating the clinical evaluation of first-generation killed SARS vaccine in Asia.

### Milestones

In 2004:

- A workshop is organized on “Animal Models for the Development of SARS Vaccines”.
- In collaboration with the WHO Regional Office for the Western Pacific and the WHO Office in China, a fact-finding mission is conducted to the People’s Republic of China. The major objective of this mission will be to identify potential areas of collaboration between WHO and China and develop a jointly supported plan of activities.
- The safety/immunogenicity phase I trials of inactivated SARS vaccines are initiated. (WHO contribution: technical advice and support).
- WHO recommendations and guidance documents in relation to regulatory aspects and biosafety in SARS-related research and clinical trials are made available.

- 
- Potential targets for new influenza vaccines are identified. (WHO contribution: technical analysis)

In 2005:

- The preclinical results are available on the immunogenicity of new influenza vaccines supported by WHO. (WHO contribution: support to selected research projects)

## 1.5 Novel vaccine delivery systems

### Purpose

To prioritize and coordinate the development of novel vaccine delivery systems and formulations that are safer and easier to administer than existing vaccines while being at least equally effective.

### Context

The scale of immunization services is expected to rise dramatically in the coming decade, partly due to the increasing number of vaccines used. Inadequate logistics, including cold-chain failures and poor geographical access have historically hampered immunization coverage in developing countries. Rendering vaccines insensitive against exposure to elevated temperatures or freezing and reducing the number of immunization contacts is therefore likely to increase the effectiveness of vaccination programmes. Moreover, unsafe injection practices that can lead to the transmission of HIV, hepatitis B, and hepatitis C, could be avoided by needle-free vaccine delivery methods that avoid or substantially reduce the need for traditional syringes. Taken together, all of the above measures have the potential to decrease the barriers often associated with low coverage and unsafe vaccination.

### Status

In the context of improving the logistics of vaccination, WHO has been investigating methods of stabilizing vaccines using cryoprotectants to reduce dependence on the cold chain. Assessment of a measles vaccine in a powder form has been supported, and the stability of measles vaccine stabilized in sugar-glass has been evaluated. Currently, WHO is assisting international partners in evaluating the cost-effectiveness of the introduction of stabilized vaccines and the challenges to this.

In addition, WHO is continuing to explore the potential of needle-free vaccine delivery systems including technologies for nasal, oral and transdermal delivery. Studies undertaken in the past aimed to obtain proof-of-principle of the technologies and to evaluate their applicability. The focus is now on supporting studies with selected priority antigens based on their potential public health benefit, with the final goal of developing the product for implementation. Depending on results from initial studies, and taking into account the impact that introducing such technology might have, selected projects will be supported for further development.

For example, after several years of facilitating research on aerosol delivery of measles vaccine, a project was launched in 2002 aimed at achieving the development and licensure of a measles aerosol vaccine. The regulatory pathway is now defined and

---

preclinical studies have been successfully completed. Phase I studies are planned for 2004.

In collaboration with international partners WHO is supporting the development and safety evaluation of improved jet-injectors. Tests to evaluate the risks of transmission of blood-borne diseases are being validated. The validated tests will be available to developers for device evaluation.

### **Milestones**

In 2004:

- A decision is reached on the safety status of multi-dose jet injectors.
- A decision is reached on the development of a projectile/implant (ballistic) subcutaneous delivery system. (WHO contribution: funding and technical support)
- At least one additional needle-free proof-of-principle study (transdermal or nasal) is undertaken.

### **Measles Aerosol**

- Preclinical studies to characterize the performance of selected nebulizers and development of criteria on which devices are completed.
- Economic analyses are completed.
- An Investigational New Drug dossier (IND) for phase I is submitted to Indian regulatory authority. (in collaboration with the Serum Institute of India)
- A phase I clinical study is completed.
- Methods suitable for Phase II clinical trials and likely trial sites are identified.

In 2005:

- A phase I/II trial is completed of a needle-free projectile/implant (ballistic) delivery system.
- Feasibility of implementing cryoprotectants to overcome vaccine freezing is assessed.

### **Measles Aerosol**

- A clinical protocol for Phase II studies is developed and reviewed.
- An IND for phase II trial is submitted to Indian regulatory authority. (in collaboration with the Serum Institute of India)
- Phase II studies are initiated.

---

## 1.6 Malaria vaccines

### Purpose

To accelerate the development and evaluation of safe and effective candidate vaccines against malaria.

### Context

Current tools for malaria control are challenged by the development of insecticide resistance and antimalarial drug resistance. More than 2000 million people or 40% of the world's population live in malaria-endemic regions. WHO estimates that there are 300–500 million clinical cases annually, making malaria the most prevalent parasitic disease. It is also the most deadly parasitic disease in the world, being estimated to cause 1.1 million deaths annually.<sup>21</sup> The need for an effective tool for prevention is clear. Since the period 30 years ago when human volunteers were immunized through being bitten by irradiated sporozoite-carrying mosquitoes, research on a vaccine against malaria has made good progress. There are high expectations that a safe, affordable, deliverable and effective malaria vaccine will be found. However, there are major obstacles to accelerated vaccine development. These include lack of funds as well as gaps in knowledge which affect critical steps along the vaccine development continuum, such as a lack of appropriate models and validated serological correlates of protective immunity.

### Status

Current vaccine candidates are predominantly cell-surface antigens found during one of the developmental stages of the parasite's life cycle in humans. There are several categories of candidate vaccines against malaria. There are pre-erythrocytic candidates which are directed against sporozoites and the liver stages of the parasites, and which are aimed at preventing infections. There are also asexual or blood-stage parasites aimed at reducing disease severity and transmission-blocking vaccines against parasite gametes. Another category is an anti-disease vaccine involving the identification of parasite toxins that contribute towards disease and subsequent neutralization and use as an agent for disease attenuation. An additional category is the multi-component vaccine candidates where antigens from different stages are combined, expressed and manufactured in a variety of available means. A parallel strategy to this involves the development of new and improved vaccine formulations either with novel adjuvants or platform technologies. These efforts are aimed at antigen delivery to the host in a formulation that will induce the desired protective immune response.

Although malaria vaccine research remains chronically underfunded, malaria vaccine development has benefited from greater public awareness of the problem, unprecedented collaboration among public and private agencies and institutions as well as scientific advances that have improved the process development of vaccine candidates, and the development and testing of novel vaccine formulations.

WHO continues to support malaria vaccine development by funding research and preclinical development of select vaccine candidates and by contributing towards

---

<sup>21</sup> *The World Health Report 2003: Shaping the future*, World Health Organization, Geneva, 2003.

---

enhancing comparability of candidate vaccines by providing good laboratory practices, good manufacturing practices and good clinical practices (GLP, GMP, GCP) materials and training, as well as guidance and independent monitoring of vaccine trials.

## Milestones

In 2004:

- Standardization is completed of Standard Operating Procedures for primate models for screening candidate malaria vaccine antigens.
- New research into improved immune correlates of protective immunity is initiated. (WHO contribution: support to selected research projects)
- At least one new malaria vaccine clinical trials site is upgraded to perform according to GCP level.
- A PfCP-2.9 Phase I clinical trial is completed and the results are submitted for publication. (WHO contribution: sponsoring of the clinical trial and design of the clinical development strategy)
- A registry is established of malaria vaccine trials sites by region and capacity (in collaboration with other malaria vaccine funding agencies).
- Minimum criteria are set for a site to conduct malaria vaccine trials.

In 2005:

- At least one immune assay useful in the selection of candidate antigens/ epitopes is standardized. (WHO contribution: support to selected research projects)
- Two Phase I and one Phase II clinical trials start. (WHO contribution: continued support of vaccine candidates into clinical trials)
- Clinical trial sites readied for efficacy trials. (WHO contribution: support for GCP training)
- Phase IIa standard model protocol for conduct of malaria vaccine efficacy trials available. (In collaboration with other malaria funding agencies)

## 1.7 Leishmaniasis vaccines

### Purpose

To accelerate the development and evaluation of candidate vaccines against *Leishmania*.

### Context

Leishmaniasis represents a group of diseases caused by more than a dozen parasites of the genus *Leishmania* with diverse epidemiology, covering anthroponotic (human-human) as well as zoonotic (animal to human) transmission. Control of vectors or reservoir is either impractical, costly or requires infrastructure beyond the means of many disease-endemic countries and hence is difficult to sustain. The first-line drugs (antimonials) are associated with toxicity, require prolonged daily injection, are costly and are becoming useless due to parasite resistance. Newer drugs are beyond the reach of most of those who need them due to their high cost and limited

---

availability. A safe, efficacious and affordable vaccine is considered to be the best control tool for all forms of leishmaniasis. A vaccine may also be used for therapy either alone or in combination with chemotherapy to reduce the dose or duration of drug treatment.

## Status

There are numerous candidate recombinant antigens with potential for development based on activity in experimental models. However, resources are insufficient to support clinical development of these candidates. The current vaccine candidates in development are very few: (i) whole parasites with or without adjuvants (still being tested for prophylaxis or treatment); (ii) a fraction of *Leishmania* membrane (Fucose-Mannose Ligand, FML) tested against visceral disease in dogs with a modest 50% reported efficacy; and (iii) a three-component single recombinant antigen (Leish-111f) with Monophosphoryl Lipid A in a stable squalene/water emulsion (MPL-SE adjuvant) in clinical phase I trials.

## Milestones

In 2004:

- The level of efficacy of Mayrink's vaccine is established and its future usefulness determined.
- A dose escalating safety and immunogenicity trial is initiated of Leish-111f+MPL-SE in healthy individuals in an endemic focus. (WHO-IDRI milestone)
- At least a two-dose escalating safety and immunogenicity trial is initiated of Leish-111f+MPL-SE together with standard antimonial treatment in patients with chronic leishmaniasis. (WHO-IDRI milestone)

In 2005:

- Sites for further trials are identified and infrastructure as well as trained human resources are put in place for trials according to GCP-ICH.
- The safety/immunogenicity of Leish-111f+MPL-SE is established and the required doses of vaccine for prophylaxis as well as for addition to chemotherapy are identified for further trials. (WHO-IDRI milestone)
- The possible usefulness of first generation heat-killed whole cell leishmaniasis vaccine adsorbed on alum and adjuvanted with BCG (Alum-ALM+BCG) as an adjunct to chemotherapy for non-responding PKDL cases in a hospital-based trial is established and if indicated a field evaluation is initiated.

---

## 1.8 Rabies immunoglobulins

### Purpose

To develop and evaluate a cocktail of rabies virus neutralizing antibodies for the treatment of rabies infection.

### Context

There is a global shortage of rabies immunoglobulins (RIG), an essential component of rabies post-exposure prophylaxis, particularly in developing countries where more than 90% of the treatments for rabies post-exposure are applied. There is therefore a need to develop a new technology that could replace RIG.

### Status

A cocktail of two or three monoclonal neutralizing antibodies has been identified as a new tool for the prevention of rabies. In the absence of other significant efforts in this area, IVR is working in partnership with WHO collaborating centres and other institutions or groups to develop a cocktail of monoclonal anti-rabies antibodies to replace RIG.

### Milestones

In 2004:

- Agreement is reached with the WHO collaborating centres on rabies research for the donation of hybridomas to the project.
- Agreement is reached with at least one manufacturer to produce monoclonal antibodies under GMP conditions using mouse hybridomas.
- A partnership is established for the engineering of humanized monoclonal antibodies in transgenic plants.

In 2005:

- Technology is developed and scaled up for the production of the therapeutic cocktail using fermentation. (WHO contribution: technical advice and partial support to the project)
- At least two humanized monoclonal antibodies are expressed in transgenic plants. (WHO contribution: technical advice and partial support)

---

# Target two

---

## IVR Target

Facilitate late-stage clinical development of appropriate formulations of new vaccines into disease-endemic developing countries.

## Expected Result

Clinical trials (safety, immunogenicity and efficacy) facilitated for selected new HIV/AIDS, pneumococcal, meningococcal, enterotoxigenic *E. coli*, Japanese encephalitis, rotavirus and Human papillomavirus vaccines, and for vaccines against other infectious diseases, where appropriate.

## Critical Indicators

- 1) Number of likely early-introducers of vaccines in low-and lower-middle income countries provided with data supporting evidence-based decisions about vaccine introduction against pneumococcus, rotavirus or HPV infection
- 2) Number of priority developing countries having progressed on their HIV vaccine preparedness activities (National Plans, training activities, infrastructure strengthening, and/or actual conduct of clinical trials)

## Status

Some vaccine candidates that would be highly desirable for low-income countries have actually reached quite an advanced stage of development. These are often vaccines that are also useful in industrialized economies and consequently their development has been geared to the requirements of these lucrative markets. The challenges here consist of assuring that such vaccines, their composition, formulation, intended mode of delivery, etc, are adequate for developing countries and accessible to them.

Together with international partners, WHO has developed global R&D agendas for each of the pathogens in this category. Examples of WHO activities identified by these agendas to accelerate the availability of the vaccines in developing countries include: demand forecasting through performance of epidemiological studies; promoting clinical trials in high-disease-burden countries; supporting in different ways clinical evaluation; strengthening the functions of national regulatory and ethical authorities; and developing novel modes of cooperation with vaccine producers that will speed up access to the new product(s) by populations in need.

Table 4.2 represents in broad terms the global state of development of each vaccine type as of December 2003, and indicates the primary targets for IVR activities.

**Table 4.2: Predominant areas of activity for Target 2**

Product	Standardization	Epidemiology	Discovery	Preclinical studies	Phase I	Phase II	Phase III
Global activities P1 <b>Pneumococcus</b>	+	+	+	+	+	+	+
IVR activities	+	+				+	+
Global activities P2 <b>Meningococcus</b>	+	+	+	+	+	+	+
IVR activities	+	+	+	+	+	+	
Global activities P3 <b>ETEC</b>	+	+	+	+	+	+	+
IVR activities		+		+	+	+	
Global activities P4 <b>Japanese enceph</b>	+	+	+	+	+	+	+
IVR activities	+				+	+	
Global activities P5 <b>HPV</b>	+	+	+	+	+	+	+
IVR activities	+	+	+	+	(+)	(+)	(+)
Global activities P6 <b>Rotavirus</b>	+	+	+	+	+	+	+
IVR activities	+	+				+	+
Global activities P7 <b>HIV/AIDS</b>	+	+	+	+	+	+	+
IVR activities	+	+				+	+

Note: ETEC enterotoxigenic *Escherichia coli*  
 HPV human papillomavirus  
 (+) provided funding available

---

## 2.1 Pneumococcal vaccines

### Purpose

To accelerate the evaluation and use of currently available and new vaccines against *Streptococcus pneumoniae* (Pneumococcus) in developing markets, including assurance of appropriate regulatory pathways and of steps to promote equitable access to new products in developing markets.

### Context

Globally, pneumonia remains a major cause of childhood mortality, accounting for approximately two million deaths annually. Most deaths are caused by bacterial pneumonia, with *Streptococcus pneumoniae* and *Haemophilus influenzae* being the predominant pathogens. Public health strategies have focused on case management using antibiotics. However, increasing rates of resistance to commonly used, inexpensive antibiotics have limited the benefits of this approach. Introduction of conjugate vaccines against *H. influenzae* type b (Hib) has been shown to result in a 20% reduction in the incidence of radiological pneumonia. An effective vaccine against pneumococcus is likely to have an even greater impact on pneumonia and consequently on childhood mortality in developing countries.

### Status

A pneumococcal polysaccharide vaccine has been available for several years but has limitations, both in terms of its inability to induce immunological memory and its poor immunogenicity in infants and young children. A 7-valent pneumococcal conjugate vaccine was recently licensed in the United States and several other industrialized countries. In a study conducted in the United States, this vaccine provided more than 90% efficacy against invasive pneumococcal disease (IPD). However, the 7-valent vaccine lacks some serotypes that are important in many developing countries. Trials of the 7-valent vaccine in the high-risk native American population in the United States and of a novel 9-valent vaccine in South Africa have recently been completed. Both studies showed high vaccine efficacy against IPD; the South African trial further showed that the vaccine had close to 60% efficacy in HIV-infected children. Trials of the 9- and 11-valent vaccines are under way in the Gambia and the Philippines, respectively, and are expected to be completed by 2005. WHO is providing scientific advice and monitoring for these trials.

In addition, some issues regarding regulatory requirements for licensure of new pneumococcal conjugate vaccines have been identified. First, there are potential scientific issues related to interference when the vaccine is administered in combination with other antigens. Second, there may be difficulties in registering of a vaccine in the country of manufacture if, for epidemiological reasons, there is no reason to use that vaccine in that country. Alternative pathways, such as licensing by another competent regulatory agency, need to be considered. Discussions are ongoing with the USA Food and Drug Administration, the European Agency for the Evaluation of Medicinal Products (EMA), and key developing country regulatory authorities to start this process.

---

Work has also begun, in collaboration with the GAVI Pneumococcus ADIP team, based at John Hopkins University in Baltimore (USA), to ensure that appropriate demand projections and financial incentives will be available to manufacturers to ensure development of and global access to these vaccines.

## Milestones

In 2004:

- At least four networks for laboratory-confirmed pneumococcal disease are established in developing countries. (WHO contribution: technical assistance. Funding for networks through ADIP)
- Initial data are available from the Mozambique study to determine the appropriateness of a generic protocol to measure the burden of pneumonia in developing countries. (In collaboration with the Children's Vaccine Programme [CVP])
- The initial phase of an evaluation of the safety of a neonatal dose of pneumococcal conjugate vaccine is completed.
- The standardization and validation of serological assays to measure immune responses for pneumococcal conjugate vaccines are completed and conclusions published.
- The two-year post-vaccine introduction surveillance is completed in at least one developing country site and in one high-risk indigenous population.

In 2005:

- Pneumonia disease burden data (using standardized WHO radiological definitions of pneumonia) are available from Mozambique and at least one other developing country. (In collaboration with CVP)
- An efficacy study of pneumococcal conjugate vaccine with radiological pneumonia as an end-point is completed in the Gambia and the Philippines. (In collaboration with other partners)
- A study evaluating the safety and immunogenicity of a neonatal dose of pneumococcal conjugate vaccine is completed in Kenya.
- Advisory groups to determine optimal vaccination schedules for pneumococcal vaccines are established in three regions.
- Regulatory pathways in principle are available for all pneumococcal vaccines at the clinical stage, including regulatory oversight to ensure quality and consistency at international level and appropriate epidemiological analysis of clinical data.
- Acceptable production sources are identified for this product, ensuring that developing country markets have access to the vaccine.

---

## 2.2 Conjugate meningococcal vaccines against serogroups A, C, W135

### Purpose

To support the development, clinical evaluation, licensing and introduction of serogroup A containing meningococcal conjugate vaccines in the “meningitis belt” countries in Africa.

### Context

African meningitis belt countries suffer from endemic meningococcal disease, primarily in children under the age of five years, at an annual attack rate of as much as 60 cases per 100,000 population. In addition, serogroup A meningococcal disease occurs in explosive epidemics predominantly throughout what is known as the “meningitis belt” of sub-Saharan Africa. The belt stretches from Ethiopia in the east, to the Gambia and Senegal in the west, with a population at risk of over 240 million. Countries within the meningitis belt suffer from recurrent meningococcal epidemics, often in irregular cycles every 5 to 12 years. Epidemics are mostly caused by serogroup A strains, although serogroup C strains also have been responsible for outbreaks. Recently, resurgence of serogroup W135 has also caused concerns. The size of these epidemics can be enormous with attack rates in the order of 400 to 800 cases per 100,000 population. In individual communities, attack rates as high as one in ten of the population have been reported.

A vaccine that can provide long-term protection in children (routine immunization) and adults (“catch-up” strategy), that can be administered at the same time as other routine vaccinations and that significantly reduces carriage could prevent epidemics and eliminate the need for emergency interventions. There are good reasons to believe that serogroup A meningococcal conjugate vaccine could do just that. The technology to produce safe and effective meningococcal conjugate vaccine for Africa has already been available for more than 10 years. Successful serogroup A/C conjugate prototypes previously evaluated in African infants were highly immunogenic, and others against meningococcal C disease have already been shown to be effective in the United Kingdom. Yet, by 1999, vaccine manufacturers halted the development of serogroup A/C meningococcal conjugate vaccine. There are several reasons to explain this. Firstly, serogroup A meningococcus is unusual in industrialized countries. The disease caused by serogroup A is largely limited to sub-Saharan Africa and some areas in the Eastern Mediterranean Region and Asia. Secondly, the market niche further shrank when some European countries decided to license a monovalent serogroup C meningococcal conjugate vaccine. Finally, the high cost of increasing conjugate vaccine production capacity and of vaccine development, and the pressure to produce conjugate vaccines with high profitability, have combined to discourage the development of conjugate meningococcal vaccine that is affordable to populations in Africa’s meningitis belt.

### Status

A new approach was needed to deal effectively with the public health problem of epidemic meningococcal disease in sub-Saharan Africa. To this end the Meningitis Vaccine Project has been created as a partnership between WHO and the PATH. It has as its central goal the elimination of epidemic meningococcal disease in the African meningitis belt through the introduction and widespread use of conjugate

---

meningococcal vaccine. A US\$ 70 million grant from the Bill and Melinda Gates Foundation funds the project. The project currently concentrates on the development of a monovalent A serogroup vaccine, as this strategy was evaluated as being the most cost-effective.

It is of note that the 2002 epidemic in Burkina Faso revealed the expansion of another meningococcal serogroup: W135. Therefore, the evolution of the epidemiology of meningococcus infection in sub-Saharan Africa will have to be monitored very closely over the next few years, in order to assess the necessity of developing a conjugate meningococcal W135 vaccine in combination with the meningococcal A vaccine.

## Milestones

In 2004:

- Regional and national epidemic meningococcal disease surveillance systems are strengthened and expanded to evaluate the importance of serogroup W135 as a potential epidemic strain in African meningitis belt countries.
- Serological assays to measure immune responses for serogroup A meningococcal conjugate vaccine are standardized and validated.
- A forecasting demand model for this vaccine is drafted in collaboration with countries, and communicated to the manufacturer to ensure adequate production capacity. (WHO–MVP milestone)
- Specifications and quality control procedures of serogroup A conjugate vaccine are completed based on the recommendations established for serogroup C conjugate vaccine.
- A GMP batch of a conjugate meningococcal vaccine is produced and quality-controlled. (WHO–MVP milestone)
- A comprehensive overview of past and actual meningococcal meningitis situation in African target countries, including the assessment of serogroup W135 as a potential epidemic strain is generated. (WHO–MVP milestone)

In 2005:

- A regional-based plan meningococcal conjugate vaccine introduction is drafted with WHO's Regional Offices for Africa and the Eastern Mediterranean. (WHO–MVP milestone)
- A phase I safety and immunogenicity study (healthy adult volunteers) of serogroup A meningococcal conjugate vaccine is completed in the producing country. (WHO–MVP milestone)
- A financing plan for A conjugate vaccine is agreed in target countries. (WHO–MVP milestone)
- A regulatory strategy for the selected product is validated. (WHO–MVP milestone)

---

## 2.3 Vaccine against enterotoxigenic *Escherichia coli* (ETEC)

### Purpose

To accelerate the development of new enterotoxigenic *Escherichia coli* (ETEC) vaccines.

### Context

In developing countries, diarrhoeal disease caused by ETEC is responsible for close to 400,000 deaths per year among children under five years of age: almost 10%–20% of the global total of deaths from diarrhoeal disease are in this age group. The laboratory diagnosis of the enterotoxigenic *E. coli* is difficult and uses molecular techniques, which means that the disease is poorly reported and detailed surveillance data are difficult to obtain from developing country settings.

### Status

Both live and inactivated oral vaccine candidates have been developed against ETEC and their evaluation and introduction in high-risk populations need to be expedited. The inactivated oral vaccine is the more advanced candidate.

### Milestones

In 2004:

- Surveillance activities for ETEC burden of disease are initiated in sub-Saharan Africa and Asia.
- A clinical trial to evaluate the killed ETEC vaccine is initiated in a developing country. (WHO contribution: technical advice and partial funding to ICDDR, Bangladesh in collaboration with Goteborg University)
- An oral, live attenuated vaccine is evaluated in a phase I/II trial by CVD. (WHO contribution: technical advice to CVD).

In 2005:

- Adult volunteer studies are ongoing to evaluate proof of principle of the immunological and potential protective role of specific colonization factors (CFs). (WHO contribution: technical assistance)
- Studies to identify distribution of important CFs are initiated in some developing countries. (WHO contribution: support for selected projects)
- An oral live attenuated vaccine phase II clinical trial is ongoing. (WHO contribution: technical assistance and partial funding)

---

## 2.4 Japanese encephalitis vaccine

### Purpose

To ensure that the live attenuated vaccine presently being made in China meets international standards and to support the development of a second-generation chimeric Japanese encephalitis vaccine. Support disease-burden assessment in the context of accelerated vaccine introduction plans.

### Context

Approximately 3.2 billion people live in countries at risk for Japanese encephalitis (JE), representing an annual at-risk birth cohort of 70 million. A very limited amount of internationally licensed inactivated vaccine is produced. Although JE viral transmission, in principle, can be modulated by interventions aimed at the mosquito vector and vertebrate amplifying hosts, the prevention of human disease by vector control or pig immunization is impractical and cannot reduce risk to the same extent as human immunization.

### Status

Only mouse-brain-derived JE vaccines are currently licensed for international use. However, there is a shortfall between global requirements and the current maximum potential production of 30 million doses per year. The large-scale deployment of a live-attenuated vaccine in China has resulted in the successful control of JE in that country. Before this vaccine could be made available outside China, however, its production and regulation would have to undergo the rigorous evaluation required by the WHO prequalification<sup>22</sup> process to ensure that it conforms to international standards. Guidelines for the production and control of the live attenuated SA14-14-1 JE vaccine have already been developed and adopted by the Expert Committee for Biological Standardization in 2000. Promising second-generation JE candidate vaccines (inactivated cell-derived, chimeric Yellow fever/JE and DNA vaccines) are now under development although licensing is unlikely in less than five years.

### Milestones

In 2004:

- The evaluation is completed of the safety and immunogenicity (phase I/II) of YF/JE chimeric vaccine in adults in a country in the Western Pacific Region. (WHO contribution: technical advice and support)

In 2005:

- Pediatric Phase I/II evaluation of the YF/JE chimeric vaccine is initiated in at least one developing country. (Technical advice and support, in collaboration with various partners)

---

<sup>22</sup> Prequalification is a rigorous and lengthy process. If successful, vaccines can be purchased by United Nations agencies for global use. A critical component of the prequalification process is a fully functional national regulatory authority.

---

## 2.5 Human papillomavirus vaccine

### Purpose

To accelerate the clinical evaluation of human papillomavirus (HPV) virus-like particles (VLPs) vaccine candidates, with a view to facilitating their introduction in developing countries, and to initiate the development of second-generation vaccine candidates for global prevention of cervical cancer.

### Context

Genital human papillomavirus infections are the most common sexually transmitted viral infections diagnosed in clinical practice. Because of its contagious nature, approximately two-thirds of all people who have sexual contact with an infected partner will develop an HPV infection within three months. Seventy per cent of genital HPV infections are subclinical, and do not progress to disease. However, there is a causal link between HPV infections and the development of cervical cancer. The prevalence of chronic infections in industrialized countries is estimated at 7% and in developing countries at 15%, equalling a total of 630 million infected people worldwide.

Although cervical cancer develops in a minority of HPV-infected women with persistent premalignant cervical lesions, it nonetheless represents around 500,000 new cases identified each year. Over half of these cases occur in Asia. This places cervical cancer second to breast cancer in terms of global cancer incidence in women. It therefore continues to be a serious public health problem worldwide. Globally 288,000 women die of cervical cancer each year with the majority of these deaths (80%) occurring in developing countries.

An effective vaccine against the major oncogenic HPV types could have a tremendous impact on the global burden of cervical cancer. This is particularly true for developing countries, where other diagnostic and therapeutic options are often not affordable or are simply unavailable.

### Status

Recombinant DNA technology has been used to produce subunit virus like particles (VLPs), against the most common oncogenic HPV types, 16 and 18. The encouraging preclinical results obtained in the *in vivo* testing of HPV VLPs have prompted both commercial and public institutions to pursue the clinical evaluation of these candidate vaccines, mostly focused on studies in the Americas. Results from phase I trials have confirmed the safety and tolerability of the recombinant viral proteins and showed excellent immunogenicity. Phase II trials have shown a homogeneous serologic immune response and very effective protection against persistent HPV infection in women. Phase III trials have started in the United States, Latin America and Asia with the aim of demonstrating efficacy in preventing high-grade cervical lesions in vaccinated women. While the current vaccine candidates are bivalent for the oncogenic HPV types 16 and 18, it may be desirable in future to have vaccines including other types, which are more prevalent in different countries or areas. More epidemiological data and analysis will help with decision-making in this regard.

---

## Milestones

In 2004:

- An analysis is conducted of the acceptability and feasibility of HPV vaccination in developing countries. (WHO contribution: paired efforts with external partners, like the Program for Appropriate Technology in Health [PATH])
- The cost-effectiveness modelling of HPV vaccination in Asia and Africa is completed. (WHO contribution: support for two studies)
- A country-specific online database is elaborated on HPV and cervical cancer burden. (In collaboration with IARC)

In 2005:

- At least two novel HPV vaccine candidates are pre-clinically tested. (WHO contribution: joint support with the US National Cancer Institute (NCI))
- Studies on HPV type prevalence are conducted in selected Asian and African developing countries with high disease burden and which lack this information. (In collaboration with IARC)

## 2.6 Rotavirus vaccine

### Purpose

To accelerate the clinical evaluation of new rotavirus vaccines and to ensure that access to developing countries and quality issues are considered as early as possible in the development process.

### Context

Rotavirus is the most common cause of severe diarrhoea in children. In developing countries, rotavirus leads to an estimated 600,000 to 700,000 deaths each year, accounting for 20%–25% of all deaths due to diarrhoea and 6% of all deaths among children less than five years of age. In industrialized countries, almost all children are infected by three to five years of age, whereas in developing countries, children are infected in their first two years of life. Usually enteric diseases are prevented through basic sanitary and hygiene measures. However, they have proved to be ineffective in reducing the percentage of diarrhoea cases due to rotavirus in industrialized countries. In fact, the same percentage of cases is reported in Finland, Sweden or the United States, as in Brazil, China or Indonesia.

### Status

The first vaccine, licensed in August 1998, was the Rhesus Rotavirus Reassortant Tetraivalent Vaccine (RRV-TV), given in three oral doses, one month apart. It provided 85% protection against severe diarrhoea and 56% protection against all diarrhoea due to rotavirus infection. WHO had started phase I evaluation in Bangladesh and in India when this vaccine was withdrawn from routine immunization in the USA in October 1999, due to a suggested association between RRV-TV rotavirus vaccination and the development of intussusception. A WHO meeting was convened in February

---

2000 to redefine research related to rotavirus in developing countries. Issues related to epidemiology, risk factors, ethics and production were discussed resulting in six major recommendations. A second vaccine is licensed for use in China.

Other candidate live attenuated oral rotavirus vaccines are under development, and two are in late stage development by multinational companies. One of these is a paediatric strain representing one rotavirus serotype. The other is a bovine-based reassortant vaccine including several serotypes of rotavirus strain.

WHO is partially supporting several projects related to three major activities (i) strain surveillance and disease burden assessment (African and Asian networks); (ii) intussusception estimation; and (iii) new oral candidate vaccine evaluation in Bangladesh, Brazil and South Africa. Several quality and safety issues need attention especially those related to the cell substrates used for production, non-target effects of vaccine in recipients and the standardization of assays, including the development of reference materials.

### Milestones

In 2004:

- Economic and disease burden estimates for rotavirus are available and documented for developing countries. (In collaboration with RVP)
- A training curriculum is in place for national regulatory authorities in potential early adopter developing countries to evaluate pre-clinical to clinical transition.
- An expert review and a national consultation are completed for economic and disease burden estimates related to rotavirus; estimates are documented and published (In collaboration with RVP)
- Phase III efficacy trials are ongoing in developing countries. (In collaboration with RVP)

In 2005:

- The phase III efficacy trial is ongoing for a second rotavirus candidate vaccine in the developing world. (In collaboration with RVP)
- Regulatory pathways are developed for live rotavirus vaccine products.
- Draft recommendations on the production and control of rotavirus vaccine are available.

---

## 2.7 HIV/AIDS vaccines

### Purpose

To promote development, facilitate evaluation, and address the future availability of preventive HIV vaccines, with a focus on the needs of developing countries.

### Context

AIDS has only been known about for 20 years, yet today it is one of the most damaging infectious diseases. It is the most common cause of death in Africa, and the fourth such cause worldwide. Approximately 3 million people died of AIDS in 2003, placing it above the other two major infectious killers, malaria and tuberculosis. Today, 38 to 42 million people are living with HIV, 95% of them in developing countries, especially in Africa, which is home to more than 25 million people living with HIV. Meanwhile, HIV continues to spread through the world. In 2003 alone more than 5 million people became infected with HIV, at a rate of more than 14 000 new infections each day.

A safe, highly effective and affordable preventive vaccine offers the best long-term hope to control the pandemic, especially in developing countries. However, a vaccine cannot be expected to completely replace other preventive interventions, especially if the first generation of vaccines have only modest protective efficacy. These vaccines would need to be delivered as part of comprehensive HIV prevention and care packages, including other health promotion and behavioural interventions, as well as policies and programmes to reduce vulnerability.

### Status

The first phase I trial of an HIV vaccine was conducted in 1987. Subsequently, more than 30 candidate vaccines have been tested in over 60 phase I/II trials, involving approximately 10,000 healthy volunteers. Most of these trials have been conducted in Europe and the USA but several have also been conducted in developing countries (Brazil, China, Cuba, Haiti, Kenya, Peru, Thailand, Trinidad and Tobago, and Uganda). The first phase III trials began in the United States in 1998 and in Thailand in 1999, to assess the efficacy of the first generation of HIV vaccines (based on the envelope protein, gp120). Results from these two phase III trials were made available in 2003, showing no efficacy in the total vaccinated population. A third phase III trial, using a prime-boost combination (canarypox-HIV vector followed by gp120), has been initiated in Thailand in 2003. In addition, numerous other HIV vaccine concepts are being explored in the laboratory and some of them are moving to phase I/II clinical trials. At least two, or perhaps three new phase III trials are expected to be initiated in several industrialized and developing countries in 2004–2005.

In this context of multiple initiatives and of the urgent need for an HIV vaccine, especially in developing countries, the new alliance proposed by the Bill and Melinda Gates Foundation (and referred to as The Global HIV Vaccine Enterprise) will be a powerful tool to scale up HIV vaccine R&D activities and to accelerate the introduction of future successful products.

---

## Milestones

In 2004:

- The advocacy strategy plan for HIV vaccine and the WHO–UNAIDS HIV Vaccine Initiative is completed.
- At least two candidate vaccines Phase I/II trials are initiated in developing countries. (WHO–UNAIDS contribution: technical advice)
- The relationship of HVI with the new HIV Enterprise is established.

In 2005:

- At least one phase III trial is launched in industrialized and developing countries, taking advantage of HVI. (WHO–UNAIDS contribution: strengthening sites in Africa, protocol review, and scientific oversight of trials sponsored by the HIV Vaccines Trials Network [HVTN])
- At least five HIV vaccine candidates Phase I/II trials are initiated in developing countries, in collaboration with WHO–UNAIDS. (WHO–UNAIDS contribution: technical advice)
- A credible estimation of future demand for HIV vaccines is available and disseminated.

---

# Target eight

---

## IVB Target

Certify all WHO regions as polio-free in 2005

## Critical Indicator

Number of WHO regions certified as polio free

## Status

The goal of the Polio Eradication Strategy is to ensure that wild poliovirus transmission is interrupted globally through coordinated international action, that the full humanitarian and economic benefits of eradication are realized, and that the lessons and infrastructure from its implementation contribute to the delivery of other health services and the control of other important diseases.

In 1988 the World Health Assembly, the annual meeting of the Ministers of Health of all member states of the World Health Organization, unanimously voted for a global effort to eradicate poliomyelitis. At the time, wild poliovirus was endemic in over 125 countries on five continents, and was a leading cause of permanent disability, paralysing in excess of 350 000 children every year.

In the 15 years since the decision was made to eradicate polio, an extensive network of national governments, international agencies, private corporations, foundations, bilateral donors, humanitarian organizations, nongovernmental organizations and development banks have formed a 'global polio partnership', spearheaded by WHO, Rotary International, UNICEF, and CDC. The close relationship between national health authorities and this international partnership allowed an extremely rapid scaling-up of eradication activities in the mid-1990s such that by the end of the decade over 575 million children were regularly being reached with OPV, through the efforts of 10 million volunteers, in every low and middle income country in the world. As a result of this Global Polio Eradication Initiative, the largest public health effort in history, the number of children paralysed by this disease fell to 1918 in 2002, with just seven countries remaining endemic for wild poliovirus at the end of that year.

The Polio Eradication Strategic Plan 2004–2008 has defined four objectives and areas of work:

- Objective 1: To interrupt wild poliovirus transmission
- Objective 2: To achieve global certification
- Objective 3: To develop policies for the post-certification era
- Objective 4: To realize the full benefits from polio eradication (Polio and Millennium Development Goals).

IVR is closely associated with the implementation of Objective 3, through the facilitation of development of new inactivated poliomyelitis vaccines (IPVs).

**Table 4.3: Predominant areas of activity of IVR for target 8**

Product	Epidemiological studies	Clinical studies	Immunological studies
Global activities			
Poliomyelitis	+	+	
IVR activities		+	

## Develop policies for the post-certification era

### Purpose

To facilitate the development and evaluation of a new IPV based on the attenuated Sabin PV strains. This is one of the activities undertaken to fulfil Target 8.4: “To realise the ultimate benefits of polio eradication through global containment of laboratory stocks and vaccine production facilities, completion of the global certification process and establishment of an international consensus on the cessation of OPV”.

### Context

The broad policy objective for the post-certification era is to minimize the future risks of paralytic poliomyelitis (including vaccine-associated paralytic poliomyelitis or VAPP) for current and future generations at the lowest possible cost. In April 2003, the Global Technical Consultative Group stated that achieving this objective would require new policies in four specific areas: 1) detection and notification of circulating polioviruses, 2) long-term biocontainment of wild and vaccine strains of poliovirus, 3) polio vaccine stockpiles and outbreak response mechanisms, and 4) routine immunization against polioviruses. This decision builds on the substantial, cross-partner programme of scientific research, operational research, communications, and consultation that is ongoing to guide the policy development for the post-certification era.

### Status

As the programme to eradicate poliovirus transmission nears its successful conclusion, increasing attention is being paid to post-certification immunization policies. When there is no incidence of poliovirus infection and global immunity starts to decline, countries will be faced with difficult decisions on when and how to stop polio immunization. Not only must the economic benefits of stopping be considered, but there is also the changing acceptability of serious adverse events associated with vaccination, the need for an effective and verified containment of polioviruses in vaccine manufacturers and laboratories, and the construction and maintenance of an emergency response stockpile that must be factored in. For those countries that decide to continue with polio immunization, even for a limited time, the choice of vaccine becomes critical. Both IPV – derived from wild poliovirus – and OPV – composed of live attenuated polio strains – pose their own particular containment risks, and each has its own uncertainties associated with future supply and demand. For new producers, particularly those in the developing world, an inactivated vaccine derived from the attenuated Sabin PV strains might solve many of the remaining issues surrounding a global post-eradication immunization policy.

---

## Milestones

In 2004

- A plan is finalized for the development of Sabin-IPV.
- A situation analysis is available of industrialized and developing countries vaccine manufacturers' intentions with regard to production of polio vaccine.

In 2005

- At least three technology transfer projects for the production of Sabin-IPV are ongoing. (WHO contribution: facilitation and technical advice)
- Potency assays are standardized.

---

# Target nine

---

## IVB Target 9.1

Reduce measles mortality and achieve regional elimination goals

### Specific Indicators

- Proportion of countries that have introduced a second opportunity for measles immunization (supplemental or routine).
- Proportion of countries achieving at least 90% measles coverage through routine immunization services; administrative coverage and coverage surveys.
- Proportion of countries in which at least 80% of districts have achieved at least 80% measles/MCV first-dose coverage.
- Proportion of countries with access to a measles-rubella proficient-accredited laboratory.

### Purpose

To provide a technical and operational framework for guiding, coordinating and monitoring measles mortality reduction and regional elimination activities at global, regional and country levels.

### Context

Although national immunization services prevent over 80 million cases of measles and 4.5 million deaths annually, it is estimated that more than 610 000 deaths still occur every year.<sup>23</sup> Globally, therefore, measles remains the leading cause of vaccine-preventable child mortality. The remaining disease burden is primarily attributable to the under-utilization of the vaccine against measles. Specific goals for reduction in measles morbidity and mortality were set by the World Health Assembly in 1989, the World Summit for Children in 1990 and the World Health Assembly in 2003, as major steps towards the eventual eradication of the disease. Subsequently, target dates for its elimination were established, of 2000, 2007 and 2010 for the Region of the Americas, the European Region and the Eastern Mediterranean Region, respectively. The aim in the African Region, the South-East Asia Region and the Western Pacific Region is to reduce measles mortality. Lessons learned in the Americas will be invaluable in helping to assess the feasibility of regional measles elimination.

### Status

WHO and UNICEF, in a concerted effort with CDC and other key partners, have developed a Global Measles Strategic Plan, 2001–2005. A global measles laboratory network has been established. However, although this is a notable achievement, there is not yet a global measles reporting system similar to acute flaccid

---

<sup>23</sup> Progress in reducing global measles deaths: 1999–2002. *Weekly Epidemiological Record*, World Health Organization, Geneva, 2004, 79: 20–1.

---

paralysis reporting. Much progress has nevertheless been made in case-based surveillance at country and regional level.

IVR's responsibility in this large project consists of overseeing its research component. The milestones outlined below correspond to activities undertaken by the Initiative.

**Table 4.4: Predominant areas of activity of IVR for target 9**

Product	Epidemiological studies	Clinical studies	Immunological studies
Global activities	+	+	+
Measles			
IVR activities	+		

### Milestones

In 2004:

- Three studies are completed on vaccination of HIV-infected children in developing countries. (WHO contribution: technical support and partial funding)
- A research project is initiated to improve the understanding of the immunologic correlates of protection.

In 2005:

- A study is completed to evaluate the role of subclinical measles infection in the transmission of measles virus. (WHO contribution: support to the project)
- A simple method for measles diagnosis using oral fluid is implemented by the WHO network of laboratories.

---

## 4.2 IVR's workplan and budget

As described under 1.6.2., the IVR workplan takes into consideration the recommendations received from the IVR Advisory Committee as well as from the other two targeted advisory groups: the TDR Scientific and Technical Advisory Committee (STAC) and the Immunization, Vaccines & Biologicals Strategic Advisory Group of Experts (SAGE). The IVR workplan is administratively and financially processed as part of the IVB Departmental workplan and budget, or as part of the TDR workplan, when relevant (Table 1.2). For HIV/AIDS vaccine R&D, a workplan prepared jointly with the UNAIDS Secretariat is incorporated into the UNAIDS unified budget and workplan.

**Table 4.5: IVR 2004–2005 activity budget by team**

IVR team	2004–2005 budget (US\$)
Research on bacterial and selected viral vaccines, as well as new delivery systems(IVR/BAC)	5 720 000
Research on HIV and HSV-2 vaccines (IVR/HVI)	3 718 000
Research on vaccines against vector-borne pathogens and acute respiratory infections (IVR/POP)	2 990 000
Director's office	885 000
<i>Total IVR</i>	<i>13 413 000</i>

---

# Annex 1:

## IVR's role, by disease

(in alphabetical order)

### **Buruli ulcer (Watchful waiting)**

Buruli ulcer, a skin disease caused by *Mycobacterium ulcerans*, is found in many parts of the world. In West Africa, it represents a significant public health problem in terms of prevalence and severity of the disease. Although disease burden is not well established, it is assumed that the relatively low absolute number of Buruli patients worldwide does not currently allow for a viable stand-alone vaccine development effort. However, this is an extremely painful disease that can only be treated surgically and that mainly affects impoverished and hard-to-reach populations. Therefore, every effort to 'piggy-back' on related TB vaccine research and evaluation activities should be made, in order to ascertain that potential opportunities are not missed. In that spirit, IVR ensures that the study of the effect of new TB vaccine candidates on Buruli ulcer will not be forgotten when TB vaccine trials are planned in Buruli-endemic areas.

### **Caliciviruses (Watchful waiting)**

The role of calicivirus infection has recently been increasingly documented. Molecular diagnostic tools have shown that human caliciviruses (HuCV) are the most common cause of outbreaks of gastroenteritis in the United States and in Europe. In developing countries, HuCV infection, as demonstrated by the acquisition of serum antibodies, is acquired very early in life, which suggests that HuCVs may also play a pre-eminent role in diarrhoeal diseases in children from developing countries. IVR will advocate for increased research on caliciviruses in developing countries to determine the actual burden of disease and the epidemiology of the infection. Pending the results of these studies, IVR would envisage facilitating the clinical evaluation of vaccine candidates in young children when these vaccines become available.

### **Cervical cancer-HPV (Facilitator)**

HPV candidates vaccines based on recombinant viral capsid proteins have shown excellent tolerability, immunogenicity, and capability to prevent HPV infections in women. Phase III trials conducted by vaccine manufacturers are under way and HPV vaccines may become available as soon as 2006. IVR's role has been to facilitate these vaccines in three ways: 1) by fostering a public-private collaborative effort for global vaccine development by promoting the clinical evaluation of vaccine candidates in developing countries; 2) by facilitating the licensing process for these vaccines in developing countries by creating reference reagents to monitor immunogenicity and prevention of infections post-vaccination; 3) by raising the awareness of HPV-related cancers and HPV vaccine research by disseminating information particularly to leading health professionals in developing countries.

---

### **Cholera (Watchful waiting)**

Cholera has been increasing in its epidemiological spread. Three oral vaccines are licensed in some countries. These products are mainly used by travellers but are now under consideration for use in public health. IVR gives its watchful attention to the further development and introduction of these vaccines. It will also support, when appropriate, the WHO unit responsible for the control of infectious diseases outbreaks (CDS) and the Global Cholera Task Force in the oversight of large demonstration projects that are currently being planned in various disease-endemic regions worldwide. Such activities will also be conducted in partnership with the International Vaccine Institute (IVI) in Seoul, Republic of Korea.

### **Dengue (Facilitator)**

Dengue viruses have dramatically spread through the world. Infection with any one of the four virus serotypes of dengue (1–4) cause DF, and the most serious cases of DHF (with a case fatality rate of 1%–5%) are associated with secondary dengue infections, partially mediated by an immunopathogenic mechanism. Current vaccine development efforts are targeted to produce tetravalent candidate vaccines, and the first generation of vaccines is based on attenuation through multiple passaging in cell cultures. A new generation of live attenuated vaccines is being developed using molecular approaches, such as using attenuated-deletion mutants of dengue virus, or the yellow fever vaccine as a vector for dengue envelope sequences. The role of IVR is to facilitate clinical trials, including standardization of laboratory methods. Of special interest is the need to assess carefully the potential risks associated with immunopathogenesis. IVR also collaborates with the newly established Paediatric Dengue Vaccine Initiative (PDVI).

### **ETEC (Facilitator)**

Enterotoxigenic *E. coli* (ETEC) diarrhoea is almost exclusively a disease of developing countries. The highest incidence of ETEC infection is found in young children between one and four years of age. An oral killed vaccine has been evaluated extensively in several settings and has been shown to be safe. Unfortunately, the protective efficacy has been disappointing in young children in developing countries. IVR will ensure maximum public health benefit by facilitating and coordinating the development and clinical evaluation of ETEC vaccine candidates in developing countries.

### **Genital herpes (HSV-2) (Watchful waiting)**

Generally, the prevalence of HSV-2 infections is increasing worldwide, although it varies from 15% to 50% according to geographic location, age, sex and behavioural practices. The public health importance of HSV-2 stems from its chronicity, its complications both physical and psychosocial and its potential transmission to the newborn child. Increased attention is being given now to HSV-2 infections because of their potential role as a cofactor for the acquisition or transmission of HIV. A number of experimental vaccines have reached different stages of clinical development, and clinical trials of glycoprotein-based candidate vaccine provided preliminary information on potential efficacy, although limited only to HSV-1 negative women. Additional research and trials are being conducted to confirm and better understand these preliminary findings.

---

### ***Helicobacter pylori* – Stomach cancer (Watchful waiting)**

Several vaccine approaches are being pursued with whole cell vaccines and various recombinant antigens (catalase, hsp, NAP, CaG, VaA, urease). Prophylactic vaccination has proved feasible in animal models (dogs, mice, ...). Several phase 1 studies have been conducted in humans, but apparently interest has been decreasing recently among vaccine manufacturers. Reasons for this decreasing involvement include uncertainty about the feasibility of eliciting protection in humans, competition between drug and vaccine approaches and lack of knowledge about the real burden of disease. In this context, IVR has classified this disease in its “Watchful waiting” category and will consider more active involvement when appropriate.

### **HIV/AIDS (Facilitator)**

A safe, effective and affordable preventive vaccine is the best long-term hope to control the HIV/AIDS pandemic. The development of such a vaccine, however, has found unprecedented scientific challenges related to the lack of information on immune correlates of protection, the genetic variability of the virus, and the unreliability of animal models. However, a number of candidate vaccines are being developed and many have been evaluated in phase I/II clinical trials. Results from the first phase III efficacy trials of a gp120 candidate vaccine revealed that the vaccine had no overall efficacy in preventing HIV infection. The most rational strategy to accelerate HIV vaccine development is to promote the simultaneous development and testing of multiple vaccine concepts, in close interaction with basic research, to ensure that scientific knowledge is gained on each step of this iterative process. IVR activities are conducted through the WHO–UNAIDS HIV Vaccine Initiative, which is implementing activities in four areas: advocacy, guidance and coordination of the international effort; promotion of the development of appropriate candidate vaccines (including those based on HIV strains circulating in developing countries); facilitation of clinical trials in developing countries through capacity-building; and exploring issues related to future access.

### **Influenza (Facilitator)**

Between 500 000 and one million deaths occur every year due to influenza virus infections, and many millions could die in the event of a future pandemic. Safe and effective vaccines exist, based on the two envelope viral proteins: haemagglutinin and neuraminidase. These proteins, however, are subject to continuous antigenic variation, which dictate the need to modify continuously the antigenic composition of the vaccines, to ensure that they are protective against the circulating strains of the virus. Minor antigenic variations are caused by point mutations (antigenic drift), but, occasionally, genetic exchange occurs between influenza viruses infecting different animal species, leading to major antigenic changes (antigenic shift) which have been associated with pandemics. IVR explores the feasibility of developing a new generation of influenza vaccines which would confront the threat of future pandemics more appropriately, including vaccines that are more broadly protective and that confer longer-lasting protection.

---

### **Japanese encephalitis (Facilitator)**

Japanese encephalitis is an untreatable mosquito-borne viral disease that periodically flares up into major epidemics in Asia. Thirty per cent of clinical cases are fatal, and many of those surviving retain neuropsychiatric disabilities. This makes JE a significant public health problem in many Asian countries. The only vaccine available is an inactivated mouse-brain-derived product developed forty years ago. There is a need for new products that are safer and more immunogenic for public health use. New generations of JE candidate vaccines are being developed, including one which uses the yellow fever vaccine as a vector for JE envelope sequences, which has shown to be very immunogenic in phase I trials. IVR's role is to continue facilitating the clinical evaluation of novel JE candidate vaccines, with a view to introducing better products into the national immunization programmes. In addition, IVR has concluded a collaborative agreement with the manufacturer of one of the second generation JE vaccines and may play an active role in the development of this vaccine in Asia.

### **Leptospirosis (Watchful waiting)**

Some inactivated leptospirosis vaccines are currently available in very limited quantity in some countries that vaccinate workers highly exposed to infection. However these vaccines are not very immunogenic, and publication of the whole *Leptospira* genome is eagerly awaited. IVR will follow attentively the evolution of this field of research and reconsider when appropriate if leptospirosis vaccines should be targeted for more intensive WHO involvement.

### **Leishmaniasis (Facilitator and Developer)**

During the past decade, the most suitable sites for field trials of vaccines and drugs against different forms of leishmaniasis have been identified and their capacities to perform clinical trials enhanced with support from WHO/TDR. In addition, several potential vaccine candidates have emerged from TDR-funded discovery research. The Leish-111f candidate leishmaniasis vaccine developed by the Infectious Diseases Research Institute and Corixa Corp., Inc, Seattle, United States, has been constructed using conserved antigens with the view of developing a vaccine against many different forms of leishmaniasis. However, this has to be tested in humans since none of the animal models has been validated so far for any of the human leishmania diseases. In view of the past commitment of TDR to the development of vaccines against leishmaniasis, it is considered both appropriate and effective that IVR plays a facilitator role for the development of these vaccines and manages clinical trials of Leish-111f vaccine in collaboration of IDRI. These efforts are sponsored by a grant to IDRI from the Bill and Melinda Gates Foundation.

### **Malaria (Facilitator and Developer)**

IVR, through its integration of the vaccine R&D activities of TDR, is committed to facilitate and accelerate the development of malaria vaccines as a global public good. This objective has been pursued over recent years through two main avenues: a vaccine discovery grant programme and a product development effort ensuring that the most promising candidate vaccines are supported up to the stage of phase I clinical evaluation. Several antigens pioneered by WHO/TDR have recently progressed to clinical testing. In spite of these encouraging results, there is an urgent need for closer collaboration between the various players and revisitation of the global malaria

---

vaccine R&D agenda. In particular, cross-cutting issues like assessment of immune correlates of protection or development and evaluation of technology platforms for malaria vaccines should be addressed in a concerted manner to build on existing synergies.

In this context, IVR intends to pursue mostly a facilitator role, but will also continue providing support for the clinical development of candidate vaccines arising from TDR's portfolio.

### **Measles (Developer)**

Substantial progress has been made in controlling measles worldwide. However, in 2000, measles was the fifth leading cause of childhood mortality, accounting for 5% of all deaths among children less than five years of age. In 2002, there were an estimated 614 000 measles deaths.<sup>24</sup> Failure to deliver at least one dose of measles vaccine to all infants remains the primary reason for the high measles morbidity and mortality. In addition to the challenges of reaching every child, injection safety is a recognized problem, particularly in developing countries. These concerns are especially important during mass immunization campaigns when millions of doses are administered in a short period of time. IVR focuses its efforts on development of new products to facilitate the delivery of measles vaccine. The IVR Product Development Group for measles aerosol vaccine will assist IVR in defining the licensing strategy and product profile. The goal of the measles aerosol project is to license at least one method for respiratory delivery of currently licensed measles vaccines. This will provide a means of administering measles vaccine that is cheaper, safer and easier than injection. In addition, IVR continues to support research activities in the areas of measles immunology and immunopathology; development and improvement of new diagnostic methods and development of new tools to assess the impact of measles immunization strategies.

### **Meningitis A, C, W135 (Developer)**

Meningitis in Africa is hyper-endemic, with the additional threat of extremely large epidemics. Existing polysaccharide vaccines have failed to control the disease. Conjugation, based on the preceding successes of both Hib and C meningococcal vaccines offers a technical solution, but market considerations led large, industrialized country vaccine manufacturers to give up developing a conjugate dedicated to Africa. This led to the partnership between IVR and PATH as developer, through the Gates-funded Meningitis Vaccine Project. The main objective of the project (Meningitis Vaccine Project; MVP) is, while continuing epidemiological surveillance, to make a meningococcal A monovalent vaccine available at low cost for Africa by 2008. In this context, IVR supports efforts to eliminate meningitis as a public health problem in Africa through innovating North-South and South-South partnerships. Specifically IVR will directly participate in implementing the clinical trials that the Meningitis Vaccine Project will conduct in Africa.

---

<sup>24</sup> Progress in reducing global measles deaths: 1999-2002. *Weekly Epidemiological Record*, World Health Organization, Geneva, 2004, 79: 20-1.

---

### **Poliomyelitis (Facilitator)**

The creation of a framework for assessing and managing the risks of paralytic polio in the post-certification era has facilitated the development of the future polio immunization policy. The risks are identified as being due either to vaccine-derived polioviruses (VAPP, cVDPV or iVDPV) or to wild polioviruses (inadvertent release from a break in containment or intentional release). One of the potential policy options being considered by some OPV-using countries for managing the risk is the use of IPV for a transitional period following OPV cessation. All the currently available IPV is manufactured from wild type-poliovirus strains. WHO has therefore developed guidelines to minimize the risk of an inadvertent release of live wild-type poliovirus from a manufacturing site. However, this risk will always be present as existing vaccine manufacturers have indicated that they will not change the seed viruses that are used. This is because IPV is included in many vaccine combinations, each of which would need relicensing if any changes were made to the IPV seed viruses. To minimize risks of future breaks in containment, WHO has recommended that any new manufacturers of IPV should base the product on the attenuated Sabin strains. WHO has to date played a facilitating role in this process by collating information on the proof of principle of this approach and by supporting studies to develop WHO reference materials for Sabin-IPV production and quality control. Several new manufacturers have expressed interest and have initiated preliminary studies. Nevertheless this process is not progressing sufficiently for a product to be available on a large scale in the near future. In the context of a world likely to be free of wild polioviruses except for those still being used in production facilities, IVR intends to continue to play a facilitator role in the development of Sabin strains-based IPV.

### **Rabies (Developer)**

The recommended post-exposure vaccination procedure for people suspected to be infected with this virus includes administration of both vaccine and rabies-specific immunoglobulins. There is now a global shortage of rabies immunoglobulin, particularly in developing countries where more than 90% of the rabies post-exposure treatments are applied. This situation is continuously worsening with major producers in the northern hemisphere discontinuing their production of heterologous (equine) rabies immunoglobulin. There is therefore a need to develop a new technology that would free countries in need from using animal-derived products that are not totally safe even if purified, and that are neither cheap nor easy to produce. In the absence of other significant efforts in this area, IVR intends to take a leading role as developer of a cocktail of monoclonal anti-rabies vaccines that could be used to replace rabies-specific immunoglobulins.

### **Respiratory syncytial virus (Watchful waiting)**

RSV is a major cause of acute respiratory infections in children worldwide, and extensive resources are invested by the private sector into the development of RSV vaccines. In developing countries, dual infection with RSV and bacterial pathogens contributes to higher case fatality. Disease enhancement following the use of a formalin-inactivated vaccine has hampered vaccine development. Although a subunit fusion protein vaccine has been shown to be immunogenic and efficacious in high-risk children and adults with prior exposure to the virus, this vaccine is not considered appropriate for use in non-immune infants because of concerns about disease enhancement. A live attenuated vaccine is under development but a

---

sufficiently attenuated vaccine strain for use in young infants is yet to be developed. IVR's role will therefore be to monitor carefully the advancement of the development of live attenuated vaccine candidates. The Initiative would envisage moving to a facilitator role to ensure parallel testing of appropriate candidates in developing countries when a suitable vaccine is identified.

### **Rotavirus (Facilitator)**

Two rotavirus vaccine candidates are in phase III clinical evaluation and several other vaccine candidates are in development. Three distinct live, oral rotavirus vaccines have shown protective efficacy of 70%–90% against severe, dehydrating rotavirus illness that might result in hospitalization and/or death, providing “proof of concept”. Two of these vaccine candidates have not yet been fully evaluated in developing countries. In this context IVR, in close partnership with the GAVI Rotavirus Vaccine Project (RVP) team, will facilitate the parallel evaluation of the more advanced rotavirus vaccine candidates in developing countries where the need is greatest. In addition, IVR plays a strategic role in coordinating and facilitating the development of internationally accepted criteria for production of vaccine lots using good manufacturing practice, the regulatory requirements for local manufacturers and conduct of clinical trials in developing countries using good clinical practice.

### **SARS (Facilitator)**

The recent identification of a new coronavirus as the etiological agent of the severe acute respiratory syndrome is another example of an emerging disease whose control may require a vaccine. IVR is monitoring the epidemiological situation and exploring alternatives to facilitate the possible development of a SARS vaccine to ensure that, once developed, it is available for use in developing countries.

### **Schistosomiasis (Watchful waiting)**

Successful vaccine development for schistosomiasis have been hindered by lack of knowledge of the type of immune response that would provide maximum levels of protective immunity. Vaccination against human schistosomiasis in animal models has given some measure of success during the last decades, although complete protection against infection was never achieved with defined purified antigens. One of those antigens (Sh28GST) has completed the phase II clinical evaluation phase in disease-endemic countries but other candidate vaccines have yet to enter the phase of clinical evaluation. In this context, it is considered that the best role for IVR would be that of “Watchful waiting”, while advocating for more investment in this field and promoting better networking of investigators involved in product development and in analysis of immune correlates of protection.

### **Shigella (Facilitator)**

Over one hundred years after the discovery of the *Shiga* bacillus, the disease caused by these bacteria continues to be a major public health problem. Increasing levels of antibiotic resistance in *Shigella* strains has also stimulated the development of several vaccine candidates. Two candidate live oral vaccines have undergone evaluation in clinical trials but require further clinical development and testing. IVR will facilitate the parallel development and evaluation of these and other recombinant vaccine candidates through phase II and phase III clinical trials in different populations.

---

### **Streptococcus group A (Watchful waiting)**

Acute infections with group A *Streptococcus* and their consequences are a major cause of morbidity, especially in developing countries. Primary and secondary prophylaxis with antimicrobials has resulted in decreases in the sequelae of group A streptococcal disease but have been difficult to implement in many developing countries. Prevention by vaccination has been hampered by the fear of inducing antibodies that cross-react with human tissues. Several new vaccine candidates are in preclinical evaluation, including multivalent M-protein based vaccines and vaccines using a variety of fibronectin binding proteins as antigens. At present, it is considered that IVR's role should be to watch carefully the development of these candidate vaccines.

### **Streptococcus group B (Watchful waiting)**

Group B *Streptococcus* is an important cause of neonatal sepsis in industrialized countries. Although existing data show low prevalence of this infection in developing countries, more recent analysis suggests that the burden may be higher than suspected. Screening during pregnancy and antimicrobial prophylaxis has resulted in a substantial decline in disease incidence in industrialized countries. However, this strategy is difficult to apply in developing countries. Moreover it does not reduce the incidence of late onset sepsis and is associated with emergence of antimicrobial-resistant pathogens. Multivalent protein conjugate vaccines containing the capsular polysaccharide have been found to be safe and immunogenic in pregnant women in phase I and II trials. However, the efficacy of the vaccines in preventing neonatal sepsis has not been proved. IVR will follow ongoing studies on disease burden and vaccine development and consider more active involvement when appropriate.

### ***Streptococcus pneumoniae* (Facilitator)**

A 7-valent conjugate vaccine against *S. pneumoniae* is licensed for use in several countries. However, the serotypes represented in this vaccine are not optimal for use in many developing countries. A formulation containing 9 serotypes has been shown to be safe and efficacious against invasive pneumococcal disease and 11-valent formulations are under evaluation. Nevertheless, the efficacy of the vaccine against pneumonia and pneumonia mortality, the outcomes of greatest public health interest in developing countries, are not well established. IVR's role, in close partnership with the GAVI Pneumococcus ADIP team, is to facilitate the evaluation of appropriate vaccine formulations in developing countries against outcomes of public health importance, thereby creating a demand for the vaccine that may lead to its becoming available in these countries at an affordable price.

### **Trachoma (Watchful waiting)**

Global elimination of trachoma as a disease of public health importance has been targeted by WHO for 2020, through a more intensive use of chemotherapeutic interventions. In addition, a subunit vaccine candidate for *Chlamydia trachomatis* is currently being developed by the private sector. This will be the first time that vaccine against trachoma has entered the clinic in 30 years. Nevertheless, at present, the science around trachoma vaccines is not considered to be sufficiently mature to justify IVR's involvement as developer of a specific candidate vaccine or as facilitator of R&D efforts.

---

### **Tuberculosis (Facilitator)**

The enormity of the TB disease burden as well as the variable efficacy of the existing vaccine (BCG) have prompted scientific efforts, often stimulated by WHO, to define an improved TB vaccine. As a result, a number of candidate vaccines of different types, such as attenuated mycobacteria or protein and DNA subunit vaccines, are now completing preclinical development. However, the transition of these academic approaches into fully-fledged industrial vaccine development is a slow process. The vaccine industry perceives many scientific and logistics risks associated with downstream development of new TB vaccine candidates. Furthermore, the future markets for such new vaccines are not easily assessed. The overwhelming proportion of TB cases is observed in low-income countries. This strongly indicates the need for the public sector to play an important role, and for WHO in particular to accelerate the full clinical evaluation, licensing and introduction of these important new products. IVR has taken up this challenge and together with international partners engages not only in advocacy, but also in activities that facilitate preclinical and clinical evaluation under standardized, equitable and ethical conditions.

### **Typhoid (Watchful waiting)**

The Vi antigen-based vaccine has showed around 80% efficacy and is licensed in more than 92 countries in Africa, Asia, Europe, Australia and the Americas. The live attenuated strain Ty21a is licensed in 56 countries in Asia, Africa, Europe and the Americas. Three new candidate vaccines are currently in late-stage development. As the International Vaccine Initiative (IVI) has taken the lead in the development of typhoid vaccines, IVR takes a watchful waiting role in this area and will support IVI's efforts when necessary.

### **West Nile Encephalitis (Watchful waiting)**

West Nile virus is a mosquito-borne flavivirus (from the same family as dengue and Japanese encephalitis viruses) that is neuropathogenic for humans, horses and birds. The virus is indigenous to Africa, Asia and Europe and what seems to be a more aggressive strain appeared in North America in 1999, and has now spread to the Caribbean. This rapid spread of the virus has spurred on vaccine development. A candidate vaccine is being developed using the yellow fever backbone technology being used for the development of other flavivirus vaccines. IVR will monitor the spread of the epidemic and the progress of vaccine development, and will envisage a more active role when appropriate.

---

# Annex 2:

## Human resources and professional backgrounds

### **Director, IVR:**

Dr Marie-Paule Kieny has a career in vaccine research and development. She was Assistant Scientific Director of TRANSGENE SA, Strasbourg, France, where she managed human or veterinary vaccine projects, and notably the development of a recombinant rabies vaccine widely used for the eradication of this disease among wild animals. Prior to joining WHO, she directed an INSERM research team working on Hepatitis C. She has published over 150 articles and reviews, mainly in the areas of infectious diseases, immunology and vaccinology.

### **Research on Bacterial Vaccines (IVR/BAC)**

Dr Teresa Aguado (Coordinator) is a Biologist and Pharmacist from Barcelona, Spain with a PhD in Immunology. She has conducted research on autoimmune diseases, immunological tolerance and immune responses at the University of Geneva, Switzerland, the University of Washington, Seattle and Scripps Clinic and Research Foundation, San Diego, California for over eleven years. In 1988 she joined WHO to manage the area dealing with generic technologies to improve vaccine efficacy and simplify vaccine delivery. From December 1998 until the establishment of the Initiative for Vaccine Research, she coordinated the activities of the Vaccine Development Team in WHO's Department of Immunization, Vaccines and Biologicals. She has many publications in the fields of immunology and vaccinology.

Dr Martin Friede, New delivery systems; Dr Uli Fruth, Mycobacterial infections; Dr Ana Maria Henao Restrepo, Aerosol measles vaccine; Dr Kader Konde, Meningococcal meningitis; Dr Sonia Pagliusi, Cancer inducing infectious pathogens; Dr Duncan Steele, Diarrhoeal diseases; Dr Marie-Pierre Préziosi, Meningococcal meningitis.

### **Research on HIV vaccines (IVR/HVI)**

Dr Saladin Osmanov (acting Coordinator) has degrees in medicine (MD) and microbiology (PhD). Until 1988, he worked as a Senior Scientist and Chief of the Laboratory of Immunodiagnosics at the Central Metchnikov Institute for Vaccines and Sera in Moscow, Russia. In 1988, he joined the WHO (Global Programme on AIDS), then UNAIDS (1995–2000), and since 2004 he has been working at the joint WHO–UNAIDS HIV Vaccine Initiative (HVI). His professional activities focused on promoting the development and evaluation of HIV vaccines, co-ordination of the global Network for HIV Isolation and Characterization, training and capacity building in preparation for HIV vaccine trials in developing countries.

---

Dr Osmanov is an author (or co-author) of more than 70 scientific articles, reviews, manuscripts and technical guidance documents in the area of HIV biomedical and vaccine-related research.

Ms Marie-Louise Chang, Ms Coumba Toure.

### **Research on parasitic and other pathogens vaccines (IVR/POP)**

Dr Thomas Cherian (Acting Coordinator and Respiratory infections) is a paediatrician specialized in infectious diseases. He took his medical degrees (MBBS, DCH, MD Paed) in India and a fellowship in Pediatric Infectious Diseases from the Johns Hopkins University, Baltimore, USA. He was a Professor of Paediatrics at the Christian Medical College, Vellore, India and a senior associate of the Department of International Health, Johns Hopkins School of Public Health. His area of research has been infectious disease epidemiology and vaccine trials, in particular on acute respiratory infections. He has been in responsible for coordinating activities in the development of vaccines against acute respiratory infections in WHO since 2000. He has over 90 publications on infectious diseases, vaccines and epidemiology.

Dr Joachim Hombach, Dengue and Japanese Encephalitis; Dr Enbo Ma, Clinical assistant; Dr Sassan Noazin, leishmaniasis; Dr Yuri Pervikov; Measles, polio and influenza; Dr Zarifah Reed, Malaria;

### **Composition of the IVR Advisory Committee in 2004**

**Dr Sujit Bhattacharya**, Director, National Institute of Cholera and Enteric Diseases, Calcutta, India

**Dr Fred Binka**, School of Public Health, University of Ghana, School of Public Health, Legon, Ghana

**Dr Michel Greco**, previously President and Chief Operating Officer, Aventis Pasteur, France, c/o Parteurop

**Dr Dan Granoff**, Senior Research Scientist, Children's Hospital Oakland Research Institute, Oakland, USA

**Dr Akira Homma**, Director, Bio-Manguinhos, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

**Dr Michel Kazatchkine**, Director, Agence Nationale de Recherche sur le SIDA (ANRS), Paris, France

**Dr John La Montagne**, Deputy Director, National Institutes of Health, National Institute of Allergy & Infectious Diseases, Bethesda, USA

**Dr Mary Ann Lansang**, Executive Director, INCLIN Trust, Manila, Philippines

**Pr Myron Levine**, Director, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, USA,

**Pr William Makgoba**, Vice Chancellor & Principal, University of Natal, Durban, South Africa

**Dr Punnee Pitisuttithum**, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand